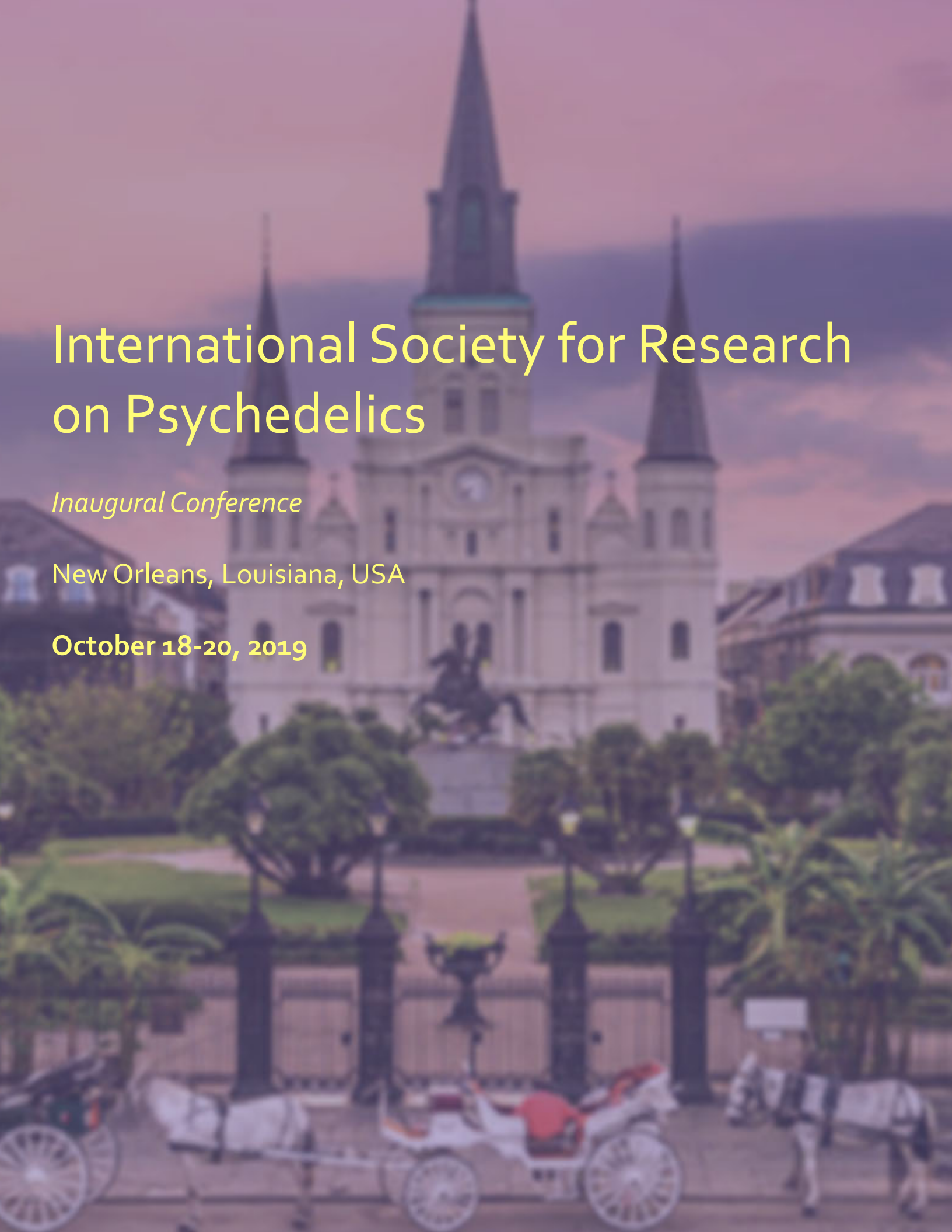

International Society for Research on Psychedelics

Inaugural Conference

New Orleans, Louisiana, USA

October 18-20, 2019

Unrestricted donations to ISRP

The ISRP would like to thank the following organizations and individuals for their generous donations to ISRP (listed in alphabetical order):

- CIIS Certificate in Psychedelic-Assisted Therapy and Research
- Heffter Research Institute with individual contributions from Robert Barnhart, George Greer, and Carey and Claudia Turnbull
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- Nichols, C
- Nichols, D

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- Peter S. Hendricks, Program Chair
- Charles D. Nichols, Secretary and local meeting organizer
- Albert Garcia-Romeu
- Paul R. Hutson
- Ben Sessa

Program committee

Hendricks (Chair), Fantegrossi, Hutson, Johnson, Murnane

Other acknowledgments

The organizers thank Alan K. Davis and Carey Turnbull for assistance with society incorporation and 501(c)(3) status.

We would also like to thank Mr. Stewart Juneau.

REGISTRATION: Thursday 3:30pm - 7pm; Friday 7:00am-12:30pm — *Table outside of Broadmore room*
Name badge, program book, and swag

*All oral presentations will be in the **Broadmore** room*

FRIDAY **General Introduction by Local Meeting Organizer**

8:30	Nichols, CD	

Session I: Anti-Inflammatory Effects of psychedelics

8:45	Nichols, CD	5-HT2A RECEPTOR AGONISTS AS ANTI-INFLAMMATORY THERAPEUTICS
9:00	*continued*	
9:15	Flanagan, TW	STRUCTURE ACTIVITY OF 5-HT2A RECEPTOR AGONISTS FOR ANTI-INFLAMMATORY PROPERTIES IN-VIVO
9:30	Guner, S	INTERACTIONS BETWEEN 5-HT2A RECEPTOR AND EGF RECEPTOR SIGNALING MODULATE EGF-INDUCED VASCULAR INFLAMMATION
9:45	Foster, T	PATHOGEN-INDUCED SEROTONIN PRODUCTION CORRELATES WITH SEVERITY OF INFLAMMATION-ASSOCIATED DISEASE:
10:00	*continued*	

Break (15 min) 10:15-10:30

Session II: Special Presentation Session from FDA and DEA

10:30	Bonson, K. et al.	DEVELOPING PSYCHEDELICS AS FDA-APPROVEDDRUG PRODUCTS
10:45	*continued*	
11:00	Carbonaro, T	THE CONTROLLED SUBSTANCES ACT: CONTROLLING OF SUBSTANCES, SCHEDULE I RESEARCHER REGISTRATION, AND HALLUCINOGENIC SUBSTANCES OF INTEREST
11:15	*continued*	

Lunch Break (75 min) 11:30-12:45 On your own

Welcoming Remarks by ISRP President Elect and President

12:45	Johnson, MW	*Presesident Elect*
1:00	Nichols, DE	*President*

Session III: Clinical - Depression

1:15	Griffiths, R	PSILOCYBIN-ASSISTED TREATMENT OF MAJOR DEPRESSIVE DISORDER: PRELIMINARY RESULTS FROM A RANDOMIZED TRIAL
1:30	*continued*	
1:45	Anderson, B	PSILOCYBIN-ASSISTED GROUP THERAPY FOR DEMORALIZATION IN OLDER LONG-TERM AIDS SURVIVORS: A SAFETY AND FEASIBILITY PILOT STUDY
2:00	Araujo, D	NEUROPHYSIOLOGICAL AND ANTIDEPRESSANT EFFECTS OF AYAHUASCA: A RANDOMIZED PLACEBO-CONTROLLED TRIAL
2:15	Barrett, F	NEGATIVE AFFECT AS A PSYCHOLOGICAL AND NEURAL MECHANISTIC TARGET FOR THE THERAPEUTIC EFFECTS OF PSILOCYBIN
2:30	*continued*	

Break (20 min) 2:45-3:05

Session IV: Clinical Aspects of Psychedlics

3:05	Garcia, A	PSILOCYBIN-OCCASIONED MYSTICAL EXPERIENCES INCREASE TRAIT SELF-TRANSCENDENCE AND CONNECTEDNESS TO NATURE: PRELIMINARY FINDINGS FROM A RANDOMIZED CONTROLLED TRIAL
3:20	Fisher, P	A SINGLE PSILOCYBIN DOSE INDUCES A LASTING INCREASE IN MINDFULNESS IN HEALTHY HUMANS, PROPORTIONAL TO CHANGE IN BRAIN SEROTONIN 2A RECEPTOR LEVELS
3:35	Ramaekers, J	NATURALISTIC STUDIES ON THE IMPACT OF 5-MEO-DMT ON HEALTH PARAMETERS AND NEUROENDOCRINE MARKERS
3:50	Mason, N	ACUTE EFFECTS OF PSILOCYBIN ON GLUTAMATE CONCENTRATION LEVELS, FUNCTIONAL CONNECTIVITY, AND SUBJECTIVE STATE: A PLACEBO-CONTROLLED EXPERIMENTAL STUDY IN HUMANS
4:05	Family, N	SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF LOW DOSE LYSERGIC ACID DIETHYLAMIDE (LSD) IN HEALTHY VOLUNTEERS
4:20	Schindler, E	PREVENTIVE EFFECTS OF A SINGLE, LOW ORAL DOSE OF PSILOCYBIN IN MIGRAINE HEADACHE
4:35	Lewis, C	ROSTRAL ANTERIOR CINGULATE THICKNESS PREDICTS THE PSILOCYBIN EXPERIENCE
4:50	Pasquini, L	SUBACUTE EFFECTS OF THE PSYCHEDELIC AYAHUASCA ON THE SALIENCE NETWORK RELATE TO INCREASED SOMESTHESIA AND AFFECT

Opening Reception - Ritz Carlton 5:30pm - 7:00pm - Mercier Terrace & Courtyard; Food provided compliments of ISRP; Cash Bar

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SATURDAY *Breakfast Provided, compliments of ISRP (see menue in Program Book): 7:30 am- 8:45 am - Location: French Quarter Bar at the Ritz-Carlton - Open to ALL registrants*

Session V: Connectivity

9:00	Ribeiro, S	SEROTONERGIC PSYCHEDELICS AS COGNITIVE ENHANCER: POTENTIAL MECHANISMS
9:15	Ornelas, I	LYSERGIC ACID DIETHYLAMIDE REGULATES SYNAPTIC PROTEINS IN HUMAN BRAIN ORGANOIDS
9:30	Doss, M	THE ACUTE EFFECTS OF INHALED SALVINORIN A ON RESTING STATE FUNCTIONAL CONNECTIVITY IN HUMANS
9:45	Preller, K	PSILOCYBIN INDUCES TIME-DEPENDENT CHANGES IN GLOBAL BRAIN CONNECTIVITY
10:00	*continued*	

Break (20 min) 10:15-10:35

Session VI: Preclinical - Depression and Animal Models

10:35	Gonzales Maesos, J	EFFECTS OF PSYCHEDELICS ON FRONTAL CORTEX STRUCTURAL PLASTICITY IN MICE
10:50	*continued*	
11:05	Hibicke, M	A SINGLE DOSE OF PSILOCYBIN, BUT NOT KETAMINE, PRODUCES PERSISTENT ANTIDEPRESSANT-LIKE EFFECTS IN A RAT MODEL OF DEPRESSION
11:20	Olson, D	PSYCHEDELICS AS INSPIRATION FOR PLASTICITY-PROMOTING NEUROTHERAPEUTICS
11:35	*continued*	

Business Meeting - Catered Lunch

11:50-1:20

Open to Full, Associate, and Affiliate members of the society ONLY. Only FULL members may make and vote on motions.
Location: Fountainbleu Room (right next to the Broadmore room where the presentations are)
Menue is listed in the Program Book
Compliments of ISRP

Session VII: 5-HT2A Cell Biology

1:20	Salerno, J	EFFECTS OF N,N-DMT ON HUMAN ASTROCYTES: IMPLICATION FOR SYNAPTOGENESIS
1:35	Karmirian, K	DIMETHYLTRYPTAMINE INCREASES PROLIFERATION OF HUMAN NEURAL CELLS IN BRAIN ORGANOIDS
1:50	Felsing, D	B-ARRESTINS MEDIATE RAPID 5-HT2A RECEPTOR ENDOCYTOSIS TO REGULATE THE INTENSITY AND DURATION OF SIGNALING
2:05	de la Fuente Revenga	NON-PSYCHEDELIC SEROTONIN 5-HT2A RECEPTOR AGONISTS: BEHAVIORAL AND FUNCTIONAL DIVERSITY IN QUIPAZINE ANALOGUES
2:20	Sherwood, A	SYNTHESIS AND BIOLOGICAL EVALUATION OF TRYPTAMINES FOUND IN HALLUCINOGENIC MUSHROOMS: NORBAEOCYSTIN, BAEOCYSTIN, NORPSILOCIN AND AERUGINASCIN

Break (20 min) 2:35-2:50

Session VII: MDMA

2:50	Dolen, G	OXYTOCIN-DEPENDENT REOPENING OF A SOCIAL REWARD LEARNING CRITICAL PERIOD WITH MDMA
3:05	*continued*	
3:20	Heifets, B	MDMA'S PROSOCIAL AND REWARDING EFFECTS REQUIRE DISTINCT NEURAL MECHANISMS
3:35	*continued*	
3:50	Feducia, A	AN OPEN-LABEL, MULTI-SITE PHASE 2 MDMA-ASSISTED PSYCHOTHERAPY TRIAL FOR SEVERE PTSD AND SUPERVISION OF NEW CO-THERAPY TEAMS

Poster Session - Reception

5:00-6:30

Open to all registered attendees
Location: Fountainbleu Room (right next to the Broadmore room where the presentations are)
Cash Bar

SUNDAY

Session IX: 5-HT2A Chemistry

9:00	Halberstadt, A	STRUCTURE-ACTIVITY RELATIONSHIPS OF PSILOCYBIN ANALOGS AT SEROTONIN 5-HT2 RECEPTOR SUBTYPES
9:15	*continued*	
9:30	McCorvy, J	PSYCHEDELIC SUPERAGONISM AND FUNCTIONAL SELECTIVITY PROFILING AT THE SEROTONIN RECEPTORS
9:45	*continued*	
10:00	Rehen, S	BIOLOGICAL EFFECTS OF B-CARBOLINES AND SEROTONERGIC PSYCHEDELICS IN HUMAN NEURAL CELLS AND BRAIN ORGANOIDS
10:15	*continued*	

Break (15 min) 10:30-10:45

Session X: Psychedelics to treat substance use disorder

10:45	Berquist, M	PILOT STUDY ASSESSING THE EFFECTS OF SELECTIVE 5-HT_{2A} RECEPTOR AGONIST 2,5-DIMETHOXY-4-IODOAMPHETAMINE (DOI) ON ALCOHOL CONSUMPTION IN LONG-EVANS RATS
11:00	*continued*	
11:15	Johnson, M	PSILOCYIBN VS. NICOTINE PATCH: RANDOMIZED COMPARATIVE EFFICACY TRIAL
11:30	*continued*	
11:45	Bogenschutz, M	UPDATE ON PSILOCYBIN-ASSISTED TREATMENT FOR ALCOHOL USE DISORDER: RELATIONSHIP BETWEEN MYSTICAL EXPERIENCE AND DRINKING OUTCOMES IN AN ONGOING, DOUBLE-BLIND PHASE-2 TRIAL
12:00	*continued*	

Concluding Remarks

12:15

POSTERS:

Anderson, T	EMPIRICALLY IDENTIFIED BENEFITS AND CHALLENGES OF LSD AND PSILOCYBIN MICRODOSING
Battaglia, D	SELECTIVE AGONISM OF THE 5HT2A RECEPTOR SUPPRESSES PROFIBROTIC GENE EXPRESSION AND FIBROBLAST TO MYOFIBROBLASTS TRANS-DIFFERENTIATION.
Billac, G	ELUCIDATING ANTI-INFLAMMATORY SAR AT THE 5-HT2A RECEPTOR
Canal, C	EXPLORING 5-HT2 RECEPTORS AS TARGETS FOR TREATING EPILEPSY IN FRAGILE X SYNDROME: A PRECLINICAL STUDY OF FMR1 KNOCKOUT MICE
Casey, A	SYNTHESIS AND STRUCTURE ACTIVITY RELATIONSHIPS OF NOVEL 4-PHENYL-2-DIMETHYLAMINOTETRALINS AT THE 5-HT2A G-PROTEIN COUPLED RECEPTOR
Fink, L	INDIVIDUAL DIFFERENCES IN IMPULSIVE ACTION AND TEMPORAL ESTIMATION: INTERACTION WITH THE SEROTONIN (5-HT) 5-HT2A RECEPTOR
Gorman, I	POSTRAUMATIC GROWTH IN MDMA-ASSISTED PSYCHOTHERAPY FOR POSTRAUMATIC STRESS DISORDER: RESULTS FROM POOLED PHASE 2 STUDIES
Lepow, L	CANDIDATE THERAPEUTIC TARGETS FOR 3,4-METHYLENEDIOXYMETHAMPHETAMINE IN THE TREATMENT OF POST-TRAUMATIC STRESS DISORDER
Kargbo, R	THE FIRST DIRECT PHOSPHORYLATION OF PSILOCIN TO PSILOCYBIN UNDER CGMP CONDITIONS
Maillet, E	ANTI-INFLAMMATORY AND PROTECTIVE EFFECTS OF TOPICAL OPHTHALMIC (R)-DOI 0.01% IN ALLERGIC CONJUNCTIVITIS AND RECURRENT INTERMEDIATE UVEITIS DISEASE MODELS IN RABBITS
Nicholas, C	PHASE I DOSE ESCALATION STUDY OF PSILOCYBIN IN NORMAL VOLUNTEERS: SAFETY AND QTC EFFECTS
Peters, J	NORIBOGAINE IS A POTENTIAL TREATMENT FOR HEROIN ADDICTION
Petranker, R	MICRODOSING FINDINGS FROM THE GLOBAL DRUG SURVEY 2019
Taylor, S	INTRODUCTION TO PSYCHEDELIC-ASSISTED PSYCHOTHERAPY: THEORY, TRAINING, RISK MANAGEMENT, AND BENEFITS
Schenberg, E	MDMA-ASSISTED PSYCHOTHERAPY FOR VICTIMS OF SEXUAL ABUSE WITH SEVERE PTSD IN BRAZIL
Wagner, A	SECONDARY OUTCOMES FROM A PILOT TRIAL OF COGNITIVE-BEHAVIORAL CONJOINT THERAPY FOR PTSD WITH MDMA
Walsh, Z.	THE INFLUENCE OF INDIVIDUAL AND COUPLE USE OF MDMA ON CONFLICT NEGOTIATION IN INTIMATE RELATIONSHIPS.

FORMATS:

30 minute oral presentation : 25 minutes of presentation + 5 minutes Q&A

15 minute oral presentation: 12 minutes of presentation + 3 minutes Q&A

Maximum Poster Size: 4' high x 6' wide (1.2 m high x 1.8 m wide)

Poster boards will be available Thursday afternoon afrer 5pm in the Fountainbleu room, and posters should be in place by 12pm Friday
Posters not removed by 1pm Sunday will be discarded

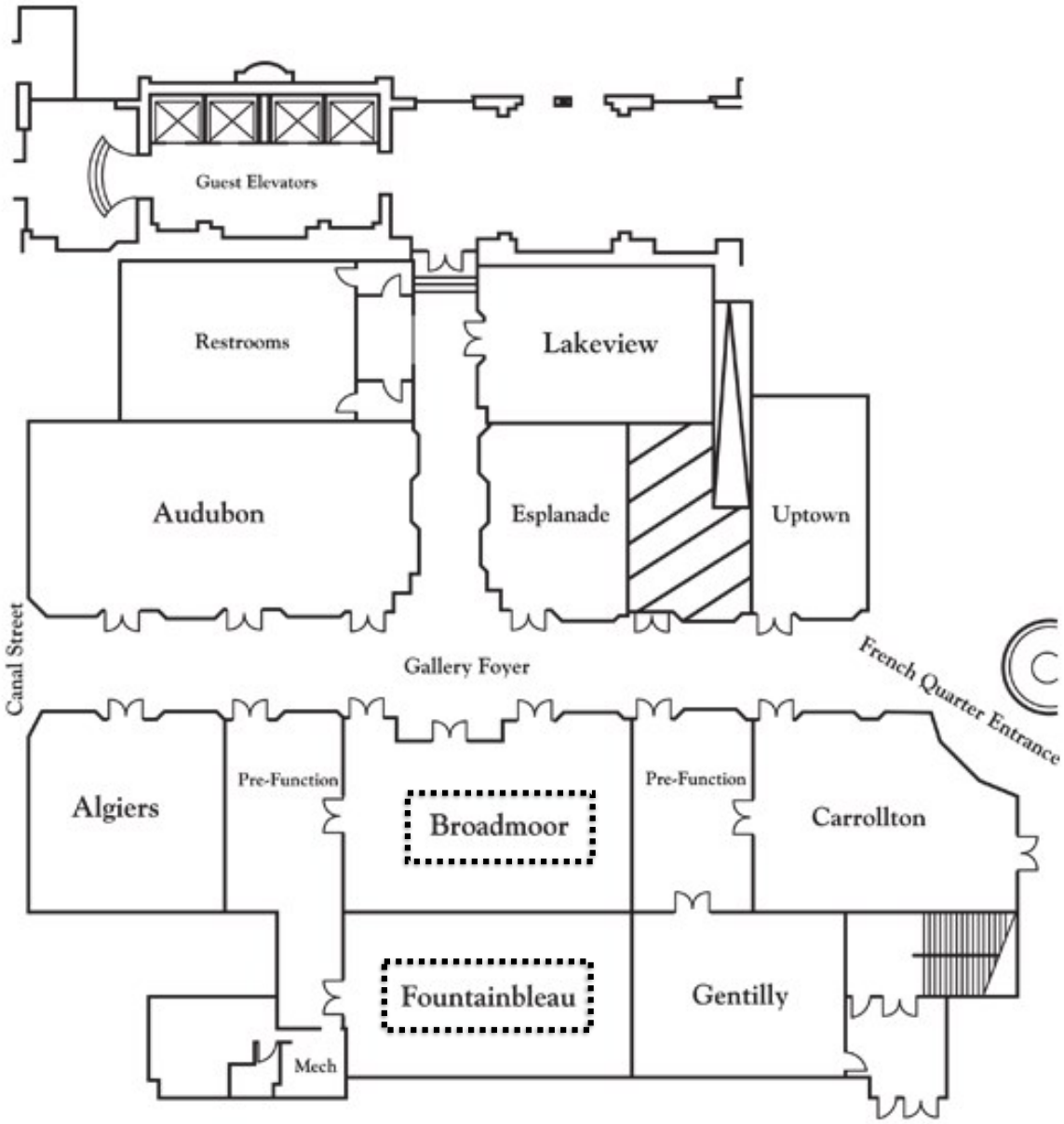
Registration will be in the hallway outside of the Broadmoor Room

Oral Sessions will take place in the Broadmoor Room

Lunch Friday for Members, and the Poster Session, will take place in the Fountainbleau Room

Coffee and Tea will be available throughout the scientific sessions in the Foyer

Floor Plan



Opening Reception

Served in the Mercier Terrace & Courtyard

Open to all registered attendees

Food Compliments of ISRP; Cash Bar

Friday (October, 18) 5:30pm -17:00pm

NOLA Taqueria

Vegetarian: Grilled Portobello, Assorted Bean and Cilantro Salad, Avocado Lime

Chicken: Mojo Roasted Chicken, Corn and Garlic Salsa, Cumin Infused Sour Cream

Pork: Adobo Pulled Pork, Pickled Red Onion, Cilantro Sour Cream

Beef: Taco de Bistec, Chayote Slaw, Jalapeno Sour Cream

Seafood: Shrimp and Crawfish Achiote, Pickled Cabbage, Lime Crema

Sides

Guacamole, Salsa, Sour Cream, Pepper Jack, Cotija Cheese, Salsa Verde

Breakfast Buffet

Served in the French Quarter Bar at the Ritz-Carlton

Provided to ALL registered attendees compliments of ISRP

Saturday (October, 19) 7:30am-8:45am

Sliced Seasonal Fruit and Fresh Berries

Individual Plain and Fruit Flavored Yogurts Homemade Granola

Fresh Baked Croissants, Danishes, and Muffins Sweet Butter and Fruit Preserves

Orange and Cranberry Juices

Freshly Brewed Coffee and Decaffeinated Coffee; The Ritz-Carlton Tea Selection

Lunch Buffet / Business Meeting

Served in the Fountainbleu room

Provided to Full, Associate, and Affiliate members compliments of ISRP

Saturday (October, 19) 11:30am-12:45pm

Local French Breads with Butter

Soup

Chicken & Andouille Gumbo with Popcorn Rice

Salads

Farm Fresh Greens, Red Onions, Kalamata Olives, Herb Roasted Croutons,
Feta Cheese Creole Mustard Vinaigrette &
Citrus Rosemary Dressing

Green Beans, Cherry Tomato, Shallot Creole Mustard Vinaigrette

Shrimp Pasta Salad, Cajun Remoulade

Entrées

Shrimp & Crawfish Étouffée, Rice Pilaf

Roasted Chicken Breast, Black Eyed Peas, Mushroom Thyme Jus

Bourbon Glazed Pork Loin, Caramelized Onion, Roasted Tomato

Crispy Cajun Potato Wedges, Garlic Butter Corn Maque Choux

Desserts

Traditional Beignets with Crème Anglaise Bananas Foster Cheesecake
Café au Lait Crème Brûlée
Praline Chocolate Tarts

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Oral Presentations

Abstracts are listed alphabetically by presenting author.

Psilocybin-assisted Group Therapy for Demoralization in Older Long-term AIDS Survivors: A Safety and Feasibility Pilot Study

Brian Anderson[1,2], Alicia Danforth[2], Robert Daroff[1,2], Christopher Stauffer[1,2], James Dilley[2], Jenny Mitchell[1,2], Josh Woolley[1,2]

1 San Francisco VA Medical Center; 2 Department of Psychiatry, UCSF

Background: Older long-term AIDS Survivors (LTAS) are people living with HIV >50 years old and who were diagnosed prior to the advent of combined antiretroviral therapy. Compared to HIV seronegative peers, LTAS suffer higher rates of depression, anxiety, trauma exposure, substance use and risky sexual behaviors. Demoralization is a syndrome common among LTAS and other palliative care patients (prevalence ~13-53%) and is characterized by poor coping and a sense of helplessness, hopelessness and a loss of meaning and purpose in life. Psilocybin is a 5HT2AR agonist and psychedelic that can improve depression and anxiety in cancer patients when combined with individual psychotherapy, possibly by enhancing the capacity of meaning-making.

Method: We conducted an open-label Phase I trial of psilocybin-assisted group therapy for gay-identified LTAS >50 years old who suffer from moderate-to-severe. Participants completed 4 preparatory group therapy visits, one psilocybin administration visit (0.3-0.36mg/kg po), and then 4-6 group therapy visits. Primary outcomes included adverse events and rate of recruitment and retention. Primary clinical outcome was change in demoralization from baseline to end-of-treatment (3 weeks post drug). Secondary outcomes included self-report measures of complicated grief, depression, and PTSD. This trial was approved by the UCSF IRB.

Results: 18 participants enrolled in the trial with 100% retention at end-of-treatment. Zero serious adverse events related to psilocybin occurred. Changes from baseline to end of treatment were found in Demoralization Scale-II (DS-II; mean difference (SD) = 6.67 (6.51), 95% CI 3.43-9.9, p=0.0004, Hedge's g=0.99); Center for Epidemiologic Studies of Depression Scale-Revised (CESD-R) (mean difference (SD) = 8.94 (14.73), 95% CI 1.62-16.27, p=0.02, Hedge's g=0.76); Inventory of Complicated Grief-Revised (mean difference (SD) = 6.22 (6.74), 95% CI 2.87-9.58, p=0.001, Hedge's g=0.52); PTSD Check List-5 (mean difference (SD) = 9 (11.47), 95% CI 3.29-14.71, p=0.004, Hedge's g=0.74). One-way ANOVA of DS-II demonstrated a main effect of F=9.04, dF=4, p<0.0001 with post-hoc Tukey pair-wise testing revealing significant differences between baseline and 1-week post drug (p<0.01), baseline and 3-weeks post drug (p<0.05) and baseline and 3-month follow-up (p<0.05).

Discussion/Significance: This was the first modern trial to demonstrate the safety, feasibility, and preliminary efficacy of a psychedelic-assisted group therapy for any disorder. Preliminary results resemble prior findings of rapid improvement in mood and anxiety symptoms in cancer patients.

Support: Sarlo Foundation, Usona Institute, Stupski Foundation, Riverstyx Foundation, Heffter Research Institute, Carey Turnbull, Saisei Foundation, UCSF AIDS Research Institute at UCSF, NIMH R25 MH060482, SFVA Advanced Neuroscience Fellowship.

Neurophysiological and antidepressant effects of ayahuasca: a randomized placebo-controlled trial

Draulio Barros de Araujo, Ph.D
Brain Institute, Federal University of RN, Natal, Brazil

Background: Since 2006 our group has been investigating the effects of ayahuasca. Our projects aim to explore the basis of the acute and sub-acute effects of ayahuasca both in healthy controls and in patients with major depression.

Methods: In a first open trial, seventeen patients with treatment-resistant depression attended a single dosing session with ayahuasca. Depression severity was accessed by two psychiatric scales (HAM-D and MADRS), before, during and after dosing. We also used Single Photon Emission Computed Tomography (SPECT) 8 hours after dosing to look for sub-acute changes of cerebral blood flow (CBF). A follow-up randomized placebo-controlled trial (RCT) was conducted in thirty-five patients with treatment resistant-depression and fifty healthy individuals. All participants were evaluated at baseline and one day after dosing to explore the effects of ayahuasca on a number of measurements, including psychiatric scales and questionnaires, and biochemical markers (cortisol, BDNF).

Results and conclusions: Both the open-label and RCT showed a significant antidepressant effect of ayahuasca already 40 min after intake, which remained significant at all endpoints up to 21 days after dosing (open-label) and 7 days after dosing (RCT). Increased blood perfusion was observed in the left nucleus accumbens, right insula and left subgenual area, brain regions implicated in the regulation of mood and emotions. Suicidality was also significantly reduced after dosing. We found basal hypocortisolemia and blunted awakening salivary cortisol response in patients with depression, compared to healthy controls. After dosing with ayahuasca, awakening salivary cortisol response was regulated to normal levels. We observed higher BDNF levels in both patients and controls that ingested ayahuasca when compared to placebo, and a significant negative correlation between BDNF levels and depressive symptoms in patients treated with ayahuasca. Evidence presented here suggests good support for the antidepressant effects of ayahuasca and other potential ramifications for its clinical use.

Studies were funded by the Brazilian National Council for Scientific and Technological Development (CNPq) and the CAPES Foundation.

NEGATIVE AFFECT AS A PSYCHOLOGICAL AND NEURAL MECHANISTIC TARGET FOR THE THERAPEUTIC EFFECTS OF PSILOCYBIN

[1]Frederick S. Barrett, Ph.D., [1]Manoj Doss, Ph.D., [1]Nathan Sepeda, B.A., [1]Roland R. Griffiths, Ph.D.

[1]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine

Background: Psilocybin has shown preliminary efficacy for the treatment of mood and substance use disorders. Enduring positive effects have also been observed up to a year after psilocybin administration in healthy individuals. Psilocybin acutely reduces sensitivity to negative affective stimuli while increasing sensitivity to positive stimuli in healthy volunteers, and reductions in negative affect have been associated with reductions in amygdala response to negative stimuli. Psychedelic effects on behavioral and neural correlates of negative affective may represent a trans-diagnostic mechanism of enduring therapeutic effects of psychedelics.

Methods: Twelve healthy volunteers in an open-label trial completed state and trait affect questionnaires and functional magnetic resonance imaging (fMRI) measures 1 day before, 1 week after, and 1 month after receiving a 25 mg/70 kg dose of psilocybin under supportive conditions. Another 12 volunteers with major depressive disorder (MDD) in an open-label trial completed clinical assessment with the GRID-Hamilton Depression Rating Scale (GRID-HAMD) and fMRI measures three weeks before the first (20 mg/70 kg) and 1 week after the second (30 mg/70 kg) of two psilocybin administrations. Outcome measures in both studies included measures of affective state and neural response to negative emotional facial expressions.

Results: Negative affect (d = 0.37-1.17) and bilateral amygdala response to negative stimuli (d = 0.77-0.79) were reduced, while positive affect (d = 0.56-1.08) and lateral prefrontal (z = 4.78) and medial orbitofrontal cortex (z = 4.75) response to conflicting emotional stimuli were increased in healthy volunteers one week after psilocybin. Negative affective and amygdala response to negative stimuli returned to baseline levels while positive affect remained elevated and trait anxiety remained reduced at 1 month post-psilocybin. Reduction in amygdala response to negative affective stimuli was also observed 1 week after psilocybin in patients with MDD, and was associated with post-psilocybin reductions in GRID-HAMD scores (r = 0.417).

Conclusion: Self-report, clinician ratings, and neural measures of negative affective processing decreased 1 week after psilocybin in both healthy volunteers and patients suffering from MDD, supporting the hypothesis that negative affect may be a mechanistic target for psilocybin.

The studies in this report were supported by National Institute on Drug Abuse grant R03DA042336 (PI: Barrett), a crowdsourced funding campaign organized by Tim Ferriss (PI: Griffiths), and by a grant from the Riverstyx Foundation. Dr. Doss was supported by a NIDA postdoctoral training grant (T32DA007209). Dr. Griffiths was supported by a NIDA grant (R01DA003889). The funding sources had no role in the design/execution of this study or the interpretation or communication of findings.

PILOT STUDY ASSESSING THE EFFECTS OF SELECTIVE 5-HT_{2A} RECEPTOR AGONIST 2,5-DIMETHOXY-4-IODOAMPHETAMINE (DOI) ON ALCOHOL CONSUMPTION IN LONG-EVANS RATS

Michael D. Berquist[1] PhD, William E. Fantegrossi[1] PhD
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Background: Alcohol use disorders (AUDs) are a significant burden to millions of Americans and have tremendous costs to society. Identifying adjunct treatments that promote long-term abstinence by reducing the motivation to consume alcohol would be highly valuable for treating individuals with AUDs. Studies in humans and rodents have shown that serotonergic psychedelics have the capacity to reduce the reinforcing effectiveness and motivational properties of alcohol; however, it is presently unknown if these effects are primarily attributable to stimulation of the serotonin 5-HT_{2A} receptor as many of these studies included compounds (e.g., lysergic acid diethylamide) that have affinity for multiple receptors. As such, we conducted a pilot study to assess the effects of the selective 5-HT_{2A} receptor agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) on alcohol consumption in rats.

Methods: Adult male Long-Evans rats (*N* = 16) were trained to orally self-administer a 20% ethanol (EtOH) solution using an intermittent access two-bottle choice procedure in their home cages. Rats received opportunities to drink EtOH during three 24-hour sessions per week in which they were presented with a bottle containing 20% EtOH and a bottle containing regular tap water. Rats always had *ad libitum* access to food. On intervening days, rats were given access to two bottles of water. EtOH consumption and preference, total fluid consumption, and food intake were measured. After reaching a stable level of EtOH intake, rats were given intermittent 24-hour access to ascending concentrations of EtOH (5, 10, 20, 40% v/v) to generate EtOH concentration effect curves (ECEC). After determination of an ECEC, the effects of naltrexone pretreatment (1 mg/kg; sc; 30 minutes before EtOH access) on EtOH intake and preference were assessed. Last, the effects of pretreatment with (*R*)-DOI (0.1, 0.32, 1 mg/kg; sc; 30 minutes before EtOH access) on EtOH intake and preference were assessed.

Results and Conclusions: Naltrexone pretreatment produced a transient reduction in EtOH intake (at 5-20% concentrations), but did not have a consistent effect on preference at the EtOH concentrations that were tested. Contrariwise, DOI pretreatment produced a longer lasting decrease in EtOH intake and a decrease in preference, which suggests that stimulation of the 5-HT_{2A} receptor may alter the motivational properties of EtOH.

Study Funded by NIH grant DA022981.

UPDATE ON PSILOCYBIN-ASSISTED TREATMENT FOR ALCOHOL USE DISORDER: RELATIONSHIP BETWEEN MYSTICAL EXPERIENCE AND DRINKING OUTCOMES IN AN ONGOING, DOUBLE-BLIND PHASE-2 TRIAL

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Background: Building on a published open-label pilot study, a randomized trial of psilocybin-assisted treatment for alcohol use disorder is currently underway, with over 80 participants randomized to date. This talk will provide an update on the status of research on psilocybin-assisted treatment for alcohol use disorder, including results of preliminary blinded analyses of drinking outcomes among the first 56 participants to complete the 12-week double-blind treatment phase of the ongoing trial.

Methods: Participants were 56 volunteers (24 women and 32 men) with DSM-IV alcohol dependence. They received 12 weekly psychosocial treatment sessions, and study medication was administered at weeks 4 and 8. Participants were randomly assigned in 1:1 ratio to receive psilocybin (25-40mg/70kg) or diphenhydramine (50-100mg). Acute effects were quantified using self-report measures including the Mystical Experience Questionnaire (MEQ) administered 7 hrs. after drug administration. Participants were separated into High-MEQ and Low-MEQ groups, based on median split of MEQ scores from the first medication session. Here we report drinking outcomes assessed at 12 weeks for the two groups. *t* tests and chi-square tests were used to contrast continuous and dichotomous outcomes, respectively, between the two groups.

Results: The median total MEQ score for the week 4 session was 0.26. The mean for the High-MEQ group was 0.65, and the mean for the Low-MEQ group was 0.06. At week 12, participants in the High-MEQ group had lower percent drinking days ($p < .05$) lower percent heavy drinking days ($p < .005$), and lower drinks per day ($p < .001$) relative to the Low-MEQ group. The high-MEQ group also had higher rates of abstinence ($p < .05$), absence of heavy drinking ($p < .05$), and treatment response, defined as ≥ 60% reduction in heavy drinking days ($p < .005$).

Conclusion: Higher MEQ Scores were predictive of improvement across a range of commonly used continuous and dichotomous drinking outcomes. While these results are encouraging, we cannot make any statements about the efficacy of psilocybin because participants were grouped according to MEQ score rather than treatment assignment, and because the definitive outcome analysis will be reported on the full sample following completion of the study.

Support: Funding for this research was provided by the Heffter Research Institute, as well as individual donations from Carey and Claudia Turnbull, Dr. Efrem Nulman, and Rodrigo Niño. Psilocybin for the study was generously provided by Usona Institute.

Developing Psychedelics as FDA-Approved Drug Products

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Background: For over 70 years, scientists have investigated the use of psychedelics to treat psychiatric conditions, including mood, anxiety, addiction, and trauma-related disorders. During the 1950s-1970s, thousands of individuals received psychedelics in clinical studies, but these investigations are unlikely to meet current Food and Drug Administration (FDA) regulations for drug studies conducted under investigational new drug (IND) applications. Thus, these older studies are best understood as providing hypotheses regarding possible medical indications for psychedelics that might be tested using modern scientific methodologies. FDA is committed to working with sponsors to determine whether a psychedelic drug is safe enough for initiation of clinical studies. FDA will also provide advice to sponsors regarding clinical trials that are intended to evaluate safety and efficacy.

Methods: Before any drug (including psychedelics) can be administered to humans, nonclinical safety studies and drug product quality evaluations must be conducted. Additional characterization may be necessary if the drug is botanically derived. Once human studies begin, there are special clinical design considerations, given the unique phenomenological effects of psychedelics. The need for psychological preparation before, during, and after treatment is an important safety component, but whether this should take the form of active psychotherapy is debated. Issues in determining efficacy include selection of the dosing regimen (e.g., “psycholytic” or “psychedelic” doses, single or repeated treatments, and length of treatment intervals), selection of endpoint measures, and evaluation of the duration of effects. When testing psychedelics, the need to maintain the blind while managing expectation bias raises issues regarding “set and setting”, patient expectations, and selection of a treatment comparator. Finally, given that most psychedelics are currently Schedule I substances under the Controlled Substances Act (CSA), a psychedelic drug product will need to be assessed for abuse potential as part of its safety evaluation. If a new drug application (NDA) for a psychedelic drug product is approved by FDA, the abuse potential assessment of the drug will inform an appropriate rescheduling action under the CSA.

Conclusion: FDA recognizes that discussion of these issues requires an active dialogue between industry, academia, and regulatory agencies. We look forward to further interaction with sponsors during the IND and NDA review processes.

The Controlled Substances Act: Controlling of substances, Schedule I researcher registration, and hallucinogenic substances of interest

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The U.S. Controlled Substance Act (CSA) of 1970 established five schedules that classify controlled substances according to how dangerous they are, their potential for abuse and addiction, and whether they possess legitimate medical value. Almost fifty years later, the CSA, though amended on several occasions, remains the legal framework from which the Drug Enforcement Administration (DEA) derived its authority. Some of DEA responsibilities include controlling and regulating licit and illicit manufacture and distribution of such substances, meeting the United States obligations under the International treaties, conventions and protocols pertaining to drug controls, and restricting the use of controlled substances to legitimate medical and scientific purposes. Utilizing available scientific data and conducting research on substances of interest is one of the ways the DEA adheres to the responsibilities of determining whether a substance meets the criteria to be controlled and which schedule is appropriate. Here, the CSA will be discussed, information and data will be provided about hallucinogenic substances of interest (i.e., 5-HT_{2A} receptor activity and drug discrimination), as well as the process to gain and maintain approval of a controlled-drug researcher registration.

Oxytocin-dependent reopening of a social reward learning critical period with MDMA

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Background: A critical period is a developmental epoch during which the nervous system is expressly sensitive to specific environmental stimuli that are required for proper circuit organization and learning. Mechanistic characterization of critical periods has revealed an important role for exuberant brain plasticity during early development, and for constraints that are imposed on these mechanisms as the brain matures. In disease states, closure of critical periods limits the ability of the brain to adapt even when optimal conditions are restored. Thus, identification of manipulations that reopen critical periods has been a priority for translational neuroscience.
Methods: Here we measured social reward learning using the social conditioned place preference (social CPP) assay in male and female mice, two days (48 hours) following treatment with MDMA, LSD, along with either ketanserin, a serotonin 2A receptor antagonist, or saline control. Roughly 30 mice were used for each condition. For electrophysiological experiments, whole cell patch clamp recordings of medium spiny neurons in the nucleus accumbens were made, and both evoked and miniature excitatory postsynaptic currents (EPSCs) were recorded before and after administration of drug in male and female mice. Between 6-10 cells were recorded for each condition. Within animal or cell comparisons of pre versus post values were analyzed using paired t-tests, whereas between animal comparisons of normalized and subtracted preference scores or normalized EPSCs were analyzed using unpaired t-tests.
Results: Here we provide evidence that developmental regulation of oxytocin-mediated synaptic plasticity (long-term depression, LTD) in the nucleus accumbens establishes a critical period for social reward learning. Furthermore, we show that a single dose of (+/-)-3,4-methylendioxymethamphetamine (MDMA) reopens the critical period for social reward learning and leads to a metaplastic upregulation of oxytocin-dependent LTD. MDMA-induced reopening of this critical period requires activation of oxytocin receptors in the nucleus accumbens, and is recapitulated by stimulation of oxytocin terminals in the nucleus accumbens.
Conclusions: These findings have important implications for understanding the pathogenesis of neurodevelopmental diseases that are characterized by social impairments and of disorders that respond to social influence or are the result of social injury.

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THE ACUTE EFFECTS OF INHALED SALVINORIN A ON RESTING STATE FUNCTIONAL CONNECTIVITY IN HUMANS

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Salvinorin A is a potent κ-opioid receptor agonist and the main psychoactive constituent of *Salvia divinorum*, an atypical dissociative hallucinogen that is used recreationally and remains unscheduled in many countries. Inhaled SA leads to a rapid onset and short duration of subjective effects that include a sense of depersonalization and derealization. Additionally, some evidence suggests a rapid antidepressant effect of SA similar to that of ketamine and psilocybin, drugs with noteworthy effects on default mode network (DMN) connectivity. In a single-blind, placebo-controlled design, we conducted the first functional magnetic resonance imaging study with acute administration of inhaled SA to explore its effects on resting state functional connectivity. Twelve healthy participants inhaled placebo (hot air) or vaporized SA (15 μg/kg) at the beginning of two separate 20-minute resting state scans. Participants listened to ambient music and wore eyeshades during each scan. Across the whole brain, SA (compared to placebo) decreased the number of significant static functional connections. This reduction in static connectivity was especially robust within the DMN during the first half of the SA scan, and persisting attenuation of the DMN during the second half of the SA scan correlated with the duration of subjective drug strength. SA was also found to decrease static connectivity within the frontoparietal network and a subcortical network that includes the salience network. An increase in functional connectivity was found between medial and lateral visual networks during SA scans, perhaps reflecting changes in visual processing. Analyses on functional connectivity dynamics, specifically variance and entropy, revealed that SA reduced variability but increased entropy across the brain, including within and between most canonical networks. However, these effects on connectivity dynamics were small, and using a leave one subject out classification procedure, we found that static connectivity alone best predicted whether a scan was collected during placebo or SA (75% accuracy), with variability and entropy adding little and sometimes even reducing classification accuracy. These findings suggest that some neural effects of SA resemble those of other hallucinogens, whereas other neural effects are unique to the altered state produced by SA.

Study was funded by National Institute of Drug Abuse (R01DA03889; T32DA007209) and Heffter Research Institute.

SAFETY, TOLERABILITY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF LOW DOSE LYSERGIC ACID DIETHYLAMIDE (LSD) IN HEALTHY VOLUNTEERS

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Background: Research has shown that psychedelics, such as lysergic acid diethylamide (LSD), have profound anti-inflammatory properties mediated by 5-HT_{2A} receptor signalling, supporting their evaluation as a therapeutic for neuroinflammation associated with neurodegenerative disease such as Alzheimer Disease (AD).

Methods: This study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered repeat dosing of microdoses of LSD. Here, we present safety and tolerability data, pharmacokinetics, and pharmacodynamic measures that relate to safety, tolerability, and dose response. This was a phase 1 double-blind, placebo-controlled, randomized study. Volunteers were randomly assigned to 1 of 4 dose groups (5 µg, 10 µg, 20 µg LSD, and placebo), and received their assigned dose on six occasions (i.e. every 4 days).

Results and conclusions: Forty-eight older healthy volunteers (mean age = 62.9 yrs), received placebo (n=12), 5 µg (n=12), 10 µg (n=12), or 20 µg (n=12) LSD. LSD plasma levels were undetectable for the 5 µg group and peak plasmatic levels for the 10 µg and 20 µg groups occurred at 30 minutes with an overall terminal half-life of 8.25 hours ± 1.6 (SE) . LSD was well tolerated and the frequency of adverse events was no higher than for placebo. Assessments of cognition, balance, and proprioception revealed no impairment.

Our results suggest safety and tolerability of microdoses of LSD every four days and support further clinical development of LSD for the treatment and prevention of AD.

This study was funded by Eleusis Benefit Corporation (USA).

An Open-label, Multi-site Phase 2 MDMA-assisted Psychotherapy Trial for Severe PTSD and Supervision of New Co-therapy Teams

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BACKGROUND: The Multidisciplinary Association for Psychedelic Studies (MAPS) completed six phase 2 clinical trials of MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder (PTSD). The FDA granted Breakthrough Therapy designation for this novel approach and agreed to plans for phase 3 trials in USA, Canada, and Israel. New therapy teams were trained for 15 phase 3 study sites. As the final step in the multi-part MAPS Therapy Training Program, new therapy teams treated one open-label participant in a phase 2 trial (MP-16) with an identical study design as phase 3, and received clinical supervision from the training team.

METHODS: An open-label phase 2 trial investigated a flexible dosing regimen of MDMA (80-120 mg) during 3 psychotherapy sessions that were each followed by 3 non-drug integrative sessions. The 12-week treatment period was preceded by three preparatory sessions. Participants with chronic PTSD and a Clinician Administered PTSD scale (CAPS-5) Total Score of ≥ 35 were enrolled (max n=60) after meeting all other inclusion/exclusion criteria. An independent rater pool administered the CAPS-5. Safety measures were collected throughout the study. The primary endpoint was two months after the third MDMA session (data collection underway until summer 2019).

RESULTS: At the primary endpoint (preliminary results), CAPS-5 total scores had significantly declined compared to baseline ($p < 0.001$, n=31) with a mean (SD) decrease of -30.3 (12.66). According to the CAPS, 80.6% did not meet PTSD criteria at the primary endpoint. Physiological vital signs and adverse event rates support an acceptable risk/benefit ratio. All new therapy teams passed the supervision phase of the training program by demonstrating competency in delivering this manualized treatment approach.

CONCLUSION: MDMA treatment was well-tolerated in these controlled clinical settings, and led to robust reductions in PTSD symptom severity. All therapy teams passed the supervision period and were well prepared for the first phase 3 trial that started in November 2018. If findings are replicated in two phase 3, MDMA-assisted psychotherapy for treatment of PTSD could be FDA-approved by 2021.

Study funded by the Multidisciplinary Association for Psychedelic Studies.

β-arrestins mediate rapid 5-HT_{2A} receptor endocytosis to regulate the intensity and duration of signaling

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Serotonin 5-HT2A receptors (5-HT_{2A}R) regulate physiological processes including platelet aggregation, smooth muscle contraction, mood and perception. 5-HT_{2A}R are the site of action for many psychedelics, atypical antipsychotics, antidepressants and anxiolytics. The 5-HT_{2A}R canonically activates heterotrimeric $G_{\alpha q}$ G-proteins which activate downstream regulators to stimulate intracellular Ca^{2+} release. The 5-HT_{2A}R also interacts with β-arrestin proteins; however, β-arrestins role in controlling efficacy and duration of 5-HT_{2A}R signaling remains largely undefined. Here we delineate contributions of β-arrestin isoforms in 5-HT_{2A}R signaling and trafficking using CRISPR/Cas9 genome editing to stably knockout (KO) β-arrestins. We first examined if agonist activation of 5-HT_{2A}R induced plasma membrane recruitment of β-arrestin using confocal imaging. Activation of HA-5-HT_{2A}R with 10uM 5-HT induced robust and rapid translocation of β-arrestin2-GFP to the plasma membrane, where it strongly co-localized with HA-5-HT_{2A}R. To determine if β-arrestins control this rapid receptor endocytosis and impact signaling, we used HEK293 cells lacking β-arrestins. Using a receptor cell surface ELISA, we confirmed 5 min agonist treatment with 5-HT or the psychedelic 2,5-Dimethoxy-4-iodoamphetamine (DOI) resulted in rapid (~50%) loss of receptors from the cell surface in parent cells; however, endocytosis was significantly reduced in β-arrestin 1/2 KO cells. Measuring kinetic live-cell Ca^{2+} release using the FLIPR assay and dose responses of selective 5-HT_{2A}R agonists, we determined prolonged duration of Ca^{2+} release in β-arrestin 1/2 KO cells. The maximal 5-HT_{2A}R calcium signaling was significantly elevated by 45% (5-HT) and 46 % (DOI) in KO cells vs. parent cells; however, agonist potency was unchanged. Re-expression of β-arrestin 1 or 2 in KO cells reduced the elevated 5-HT_{2A}R Ca^{2+} responses to that of parent cells, indicating specific effects of the genetic knockout. In addition, knockout of β-arrestin1/2 increased and prolonged duration of 5-HT_{2A}R-mediated ERK phosphorylation. This study indicates β-arrestins rapidly interact with 5-HT_{2A}R and profoundly limit both intensity and duration of $G_{\alpha q}$-mediated signal transduction. Moreover, these results indicate rapid 5-HT_{2A}R endocytosis, during agonist activation, is dependent on β-arrestins, which likely limits receptor and agonist signaling. Using the robust CRISPR/Cas9 KO model, future studies will examine downstream signaling to further define β-arrestins role in regulating 5-HT_{2A}R agonist and antagonist signaling and pharmacology.

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A single psilocybin dose induces a lasting increase in mindfulness in healthy humans, proportional to change in brain serotonin 2A receptor levels

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Abstract: Psilocybin is a serotonin psychedelic and a growing literature supports its potential efficacy in treating major depressive disorder and other neuropsychiatric illnesses. Although psilocybin evokes acute subjective effects (altered state of consciousness, weakened sense of self/ego), human studies find positive effects on clinical symptomatology and personality lasting for months. No studies to date have probed neuromolecular mechanisms mediating these lasting effects in humans; acute psychedelic effects are mediated by brain serotonin 2A receptor (5-HT2AR) signaling. We evaluated a single psilocybin dose effect on lasting changes in brain 5-HT2AR, personality traits openness and trait mindfulness.

Ten healthy and psychedelic-naïve participants (4F, 28 ± 3 years) completed a single psilocybin session (0.2 or 0.3 mg/kg). Sessions were held in a private room, facilitated by experienced support personnel. On a preceding day, participants completed a baseline [^{11}C]Cimbi-36 positron emission tomography brain scan to assess neocortex 5-HT2AR levels (BP_{ND}) and the self-report NEO PI-R and MAAS questionnaires to assess personality trait openness and mindfulness, respectively. One-week after the psilocybin session, participants completed a follow-up [^{11}C]Cimbi-36 scan. Twelve-weeks after the session, participants again completed the NEO PI-R and MAAS questionnaires. Change in 5-HT2AR levels and questionnaires were assessed using a paired t-test.

Following psilocybin administration, trait mindfulness was statistically significantly increased (Hedge's g: 0.66, p=0.004) and, consistent with previous reports, so was personality trait openness (Hedge's g: 0.23, p=0.04). At a group level, brain 5-HT2AR levels were unchanged after one-week (Hedge's g: 0.09, p=0.7). Notably, a *post hoc* examination evidenced a negative association between change in MAAS and change in 5-HT2AR (R^2=0.5, p=0.05).

We report the novel observation that a single psilocybin dose induces a lasting increase in trait mindfulness. Further, we replicate the finding of increased trait openness. Although neocortex 5-HT2AR levels were not changed at one-week, subject-specific changes correlated with change in mindfulness, suggesting relevance for lasting behavioral effects. These findings argue against a unidirectional 5-HT2AR effect of psilocybin, but suggest individual neuromolecular responses may underlie lasting trait effects. Together, these findings provide critical and novel insight into the neurobiological mechanisms mediating the lasting effects of psilocybin.

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Structure activity of 5-HT2A receptor agonists for anti-inflammatory properties in-vivo

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A screening method based on whole-body plethysmography was developed to test which psychedelic class and which 2C phenethylamine structural analog best imparts anti-airways hyperresponsiveness in a rodent acute asthma model. As rats have both an enzymatic and metabolic profile similar to humans, the use of Brown Norways allowed our lab to test numerous compounds (tryptamines, indoleamines, etc.) not possible in other conventional models. Following a two-week sensitization protocol, animals were challenged for 30 minutes thrice weekly with chicken egg albumin. In a select group of animals, rats were exposed intranasally for 15 minutes to a variety of 5-HT_{2A} agonists 30 minutes prior to allergen exposure. Whole-body plethysmography was then utilized to evaluate the ability of each compound to prevent elevated enhanced pause. While all psychedelic classes exhibited varying degrees of anti-inflammatory propensity, it is the 2C class that demonstrates the most robust and consistent AHR lowering properties. Furthermore, changes to both the 4-position and methyl-side chain of phenethylamines can have profound consequences for therapeutic efficacy. Overall, this demonstrates a high-throughput method to assess the beneficial properties of nasally-inhaled psychedelic compounds in an acute model of asthma.

Support for our work comes from a sponsored research contract from the Eleusis Benefit Corporation, and a Scholar Award from the American Asthma Foundation awarded to Charles D. Nichols.

Pathogen-Induced Serotonin Production Correlates with Severity of Inflammation-Associated Disease: Potential of 5HT2A Receptor Agonists as Therapeutics for Pathogen-Mediated Inflammatory Disease.

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Background: Pathogen-associated diseases are a complex interaction between pathogen replication and host-mediated immune responses. Although anti-infectives inhibit pathogen replication, they fail to control deleterious host inflammatory responses. Complicating this issue, use of steroidal anti-inflammatories are often contraindicated as they exacerbate rather than resolve disease. As obligate intracellular pathogens, viruses are dependent on host cell metabolism. Specifically, metabolism of the essential amino acid tryptophan, which is a prerequisite for serotonin production, is crucial for both pathogen replication, as well as host immune responses. Despite the well-defined effects of serotonin in the brain, the extensive role of peripheral serotonin (5HT) in disease-promoting inflammation is only recently being established. Many of the immune cells affected by 5HT have critical roles in perpetuating pathogen-associated chronic diseases. Therefore, we hypothesized that pathogens upregulate localized 5HT levels thereby inducing chronic inflammation-associated disease processes. Therefore, we explored 5HT2A receptor agonists as potential novel therapeutics that could suppress inflammatory processes without promoting pathogen-mediated disease.
Methods & Results: The effect of major pathogens on amino acid metabolic pathways was assessed by RT-PCR arrays. Following infection, serotonin-associated tryptophan metabolic pathways were upregulated by all pathogens examined, including the rate-limiting 5HT synthesis TPH-2 enzyme. Correspondingly, viral infection increased serotonin production both *in vitro* and in an *in vivo* model of herpetic keratitis. Ocular 5HT levels correlated with inflammation-associated clinical scoring, indicating an association of virus-induced serotonin production with clinical disease progression. Animals treated with the 5HT2A receptor agonist R-DOI, exhibited reduced viral replication and reactivation, decreased intraocular pressure, decreased neurological-associated disease, and a reduction in clinical parameters associated with chronic inflammatory disease processes. Complementary *in vitro* studies have indicated that 5HT2A receptor agonism by R-DOI can decrease inflammatory cytokine production and immune cell activation, suppress disease-promoting neovascularization, and decrease vision-threatening fibrosis. Each of these inflammatory components are contributing factors to multiple chronic inflammation-associated ocular diseases.
Conclusions: Pathogen-induced 5HT production plays a central role in subsequent development of chronic inflammation-associated disease processes, including hypertension, cell-mediated inflammation, neovascularization,vascular leakage and fibrosis. Modulation of these processes through the 5HT2A receptor represents a novel therapeutic target for treatment of numerous ocular inflammatory diseases.

Study Funded by Eleusis Benefit Corporation and the National Institutes of Health P30GM103514.

Non-psychedelic serotonin 5-HT_{2A} receptor agonists: Behavioral and functional diversity in quipazine analogues

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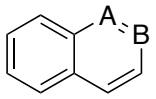
Abstract:
Quipazine is a serotonin 2A receptor (5-HT_{2A}R) agonist and anecdotal psychedelic drug originally developed as a potential antidepressant. With regard on its psychedelic-like properties, previous reports showed that this drug is able to produce generalization for DOM stimulus and induce head-twitch response (HTR) in rodents. Consistent with these findings, our preliminary data showed that quipazine induces changes in the expression of *c-fos*, *egr-1* and *egr-2* via 5-HT_{2A}R comparable to that of classic phenetylamine and tryptamine psychedelics. Compelled by this finding, we characterized the binding and functional profile of a small series of piperazine-bearing analogues of quipazine (see table below) in HEK293 cells stably expressing 5-HT_{2A}R. All analogues showed greater affinity (10^{-7}-10^{-6} M) for 5-HT_{2A}R than quipazine (10^{-5} M) in the [^{3}H]ketanserin binding displacement assay. At the functional level, only quipazine, 1NP and 2NP induced ketanserin-sensitive Ca^{2+}-mobilization. In C57 male mice, all compounds characterized as potential 5-HT_{2A}R agonists increased HTR response with the only exception of 1NP. In spite of its apparent 5-HT_{2A}R agonism, 1NP was found to block both spontaneous HTR in mice treated with vehicle and HTR-induced by quipazine. We also show that this effect was not reversed by the 5-HT_{1A}R agonist WAY100635. A previous report reported that 2NP produced generalization for DOM while 1NP did not; matching the profile we observed for these drugs in HTR. Some known 5-HT_{2A}R agonists, such as lisuride and ergotamine, are known to lack psychedelic effect in human or HTR-inducing properties in rodents, however the amount of examples is scant and limited to analogues of LSD. Further work will aim to determine whether the divergent behavioral effects of 1NP compared to 2NP and quipazine observed in mice are the result of interactions with receptor systems other than 5-HT_{2A}R or related to biased-signaling via 5-HT_{2A}R like in the case of LSD and lisuride.



General structure

Name and substituents
Quipazine: A=N, B=C-(piperazin-1-yl)
Isoquipazine: A=C-(piperazin-1-yl), B=N
2NP: A=CH, B=C-(piperazin-1-yl)
1NP: B=C-(piperazin-1-yl), A=CH

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PSILOCYBIN-OCCASIONED MYSTICAL EXPERIENCES INCREASE TRAIT SELF-TRANSCENDENCE AND CONNECTEDNESS TO NATURE: PRELIMINARY FINDINGS FROM A RANDOMIZED CONTROLLED TRIAL

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Background: Healthy volunteers who had a psilocybin-occasioned mystical experience in the laboratory showed increased personality openness lasting more than a year after drug administration. Ayahuasca users score higher than non-ayahuasca using controls on trait self-transcendence (ST), a measure of identification with the world as a unified whole. Associations between psychedelic use and nature relatedness have also been reported, but no randomized trial data exist on psychedelics' impact on ST and nature relatedness.

Methods: In an ongoing clinical trial, 50 treatment-seeking cigarette smokers were randomly assigned to receive a single high-dose (30 mg/70 kg) of psilocybin (n=25) on their target quit date (TQD), or an 8-10 week course of nicotine patches (n=25), with both groups receiving matched cognitive behavioral therapy for smoking cessation. Participants completed the Temperament and Character Inventory Revised ST subscale and Connectedness to Nature Scale (CNS) at screening, and 1 and 8 weeks post-TQD.

Results: Independent samples t-tests showed no between group differences on scores of ST and CNS at screening or 1-week post-TQD. However, change scores from baseline to 8-weeks post-TQD in ST ($p=.03$) and CNS ($p=.005$) were significantly greater in the psilocybin vs. patch group. Furthermore, splitting the psilocybin group into those who had a "complete mystical experience" (n=13) and those who did not (n=12), ANOVA showed no differences at screening on ST and CNS between the 3 groups (patch, mystical, and non-mystical experience), but revealed significant between groups differences on ST and CNS change scores at 1-week and 8-weeks post-TQD. Specifically, at 1-week post-TQD the mystical experiencers had significantly increased ST compared to patch ($p<.05$) and non-mystical ($p=.02$) groups, and significantly greater CNS than non-mystical experiencers ($p=.04$). At 8-weeks post-TQD mystical experiencers had significantly greater increase in ST ($p=.01$) and CNS ($p=.001$) than patch group.

Conclusion: Psilocybin-occasioned mystical experience can lead to persisting increases in trait self-transcendence and connectedness to nature, consistent with prior data on psychedelics' effects on personality openness and nature relatedness. Findings further support the role of psychedelic-occasioned mystical-type experience in facilitating lasting changes in personality and attitudes, and highlight potential benefits of psychedelics beyond clinical applications, which warrant additional investigation.

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EFFECTS OF PSYCHEDELICS ON FRONTAL CORTEX STRUCTURAL PLASTICITY IN MICE

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Background: Depression is associated with reduction of synaptic density in brain regions that regulate mood and cognition, including the frontal cortex. Antidepressants can reverse these neuronal deficits, although typical antidepressants have limited effect and delayed response. A notable recent discovery shows that the psychedelic drug psilocybin exerts fast-acting and long-lasting antidepressant actions in patients suffering from major depression. Despite these striking effects, a number of alterations in various mental domains, including sensory perception and thought processes, preclude the use of psilocybin and other psychedelics in daily clinical practice. Therefore, there is a clear need for basic and translational research focused on understanding the molecular and synaptic plasticity mechanisms underlying the potential clinical use of psychedelics in patients with depression, with the ultimate goal of developing safer, more effective and non-psychedelic treatment strategies.

Methods: For cortical synaptic remodeling assays, adult male mice received intra-frontal cortex injections of the AAV8 vector encoding eYFP under the *CaMKIIa* promoter, and spine structure assays were carried out three weeks after viral injection. Mice were injected with the psychedelic DOI (2 mg/kg) or vehicle, and sacrificed for analysis after 24h. Forced-swim behavior as a model of despair or passivity was assessed at least 24h following DOI or vehicle administration.

Results and Conclusions: As a general rule, increased synaptogenesis and functional synaptic plasticity are tightly correlated with the size and the shape of a dendritic spine; stubby spines are theorized to be transitional structures that enlarge, possibly into mature mushrooms spines, whereas thin spines are highly dynamic and likely change in response to activity. Our preliminary data suggest that a single injection of DOI increased the density of stubby spines in CaMKIIa-positive frontal cortex neurons, but not that of thin or mushroom spines. Overall, we also observed an increase in total spine density. Our preliminary data also suggest that DOI reduced immobility in the forced-swim test. Together, these data suggest that a single dose of the psychedelic DOI induces fast-acting effects on dendritic spine structure and remission of behavioral states associated with depression. Additional studies will test whether these effects are mediated via the serotonin 5-HT_{2A} receptor.

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PSILOCYBIN-ASSISTED TREATMENT OF MAJOR DEPRESSIVE DISORDER: PRELIMINARY RESULTS FROM A RANDOMIZED TRIAL

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Background: Major Depressive Disorder (MDD) is a prevalent condition that confers substantial public health burden. Current approved treatments are limited in effectiveness and adherence. Recent evidence suggests that one or two administrations of psilocybin with psychological support produces antidepressant effects in cancer and treatment-resistant depression populations.

Methods: This is a randomized waitlist control trial investigating the immediate and enduring antidepressant effects of two psilocybin administration sessions (20 and 30mg/70kg on sessions 1 and 2, respectively) with nondirective psychological support in patients diagnosed with MDD. Outcome measures include the GRID-Hamilton Depression Rating Scale (GRID-HAMD) scores at Baseline ($\geq$17 required for enrollment) and 1- and 4-weeks post psilocybin sessions.

Results: Twenty-one (of 24) participants have completed the intervention and the 1- and 4-week post psilocybin assessments (Mean age=40, SD=12; female=67%; Mean GRID-HAMD=23, SD=3.6; Mean Years w/Depression=21.5, SD=12.2). There were no differences in mean GRID-HAMD scores between immediate treatment (IT) and delayed treatment (DT) conditions at baseline (M_{IT}=22.9, SD=3.6; M_{DT}=23.0, SD=5.6) but there were significant differences between conditions at 1-wk (M_{IT}=7.9, SD=7.2; M_{DT}=23.8, SD=5.4; effect size: *d*=2.5) and 4-wk (M_{IT}=8.4, SD=5.7; M_{DT}=23.9, SD=5.6; effect size: *d*=2.7). The effect sizes for this intervention are more than three-times over the threshold needed to be considered a "large" treatment effect. The proportion of participants in the delayed condition meeting criteria for clinically significant response ($\geq$50% decrease in depression scores) or remission (<7 GRID-HAMD) from depression during the delay was 0% compared to those in the immediate treatment condition at 1-wk (62% response, *p*<.01; 39% remission, *p*<.05) and 4-wk (62% response, *p*<.01; 39% remission, *p*<.05). No serious adverse events were reported within 24 hours of psilocybin administration. Non-serious adverse events (within 24 hours) included headache (n=18), chest pressure (n=1), dizziness (n=1), visual distortion (n=1), stiffness/soreness (n=1), and mild controllable repetitive muscle motion (n=1).

Conclusions: These preliminary data extend previous studies in depressed cancer patients and patients with treatment-resistant depression by suggesting that psilocybin may be efficacious for treatment of MDD in the general population. Future analyses will include long-term follow-up assessment at 3, 6, and 12-months.

The study was supported by a crowdsourced funding campaign organized by Tim Ferriss and by a grant from the Riverstyx Foundation. Dr. Davis and Dr. May were supported by a NIDA T32 postdoctoral training grant (#DA007209). Dr. Griffiths was supported by a NIDA grant (R01DA003889). The funding sources had no role in the design/execution of this study or the interpretation or communication of findings.

INTERACTIONS BETWEEN 5-HT2A RECEPTOR AND EGF RECEPTOR SIGNALING MODULATE EGF-INDUCED VASCULAR INFLAMMATION

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Background: 5-HT_{2A} receptors are the main subtype expressed in vascular tissues and can mediate both vasoconstriction and inflammation. The selective 5-HT_2 receptor agonist (*R*)-DOI has known potent anti-inflammatory effects on vascular tissues. We have previously found that 5-HT_{2A} receptor activation can trans-activate epidermal growth factor receptors (EGFR) and that this EGFR transactivation contributes to vascular contractility. Furthermore, EGF and EGFR signaling can produce pro-inflammatory and anti-inflammatory effects in various tissues and experimental models, and we have found that (*R*)-DOI is able to potently prevent the effects of EGF on inflammation.

Methods: We used thoracic aortic tissues obtained from adult rats in ex-vivo preparations. Aortic pieces were pre-incubated with (*R*)-DOI (0.1-10nM) for 30 minutes followed by stimulation with EGF (10 nM) for 1 or 6-hours. Tissues were then snap frozen, and processed for RNA and protein. Expression of inflammatory markers like VCAM, ICAM, and IL6 were analyzed by qRTPCR.

Results and Conclusions: Our results show that EGF can induce two different effects on inflammatory marker expression. In one experimental system using older Brown Norway rats, EGF decreased inflammatory marker expression at 1 hour, which then became increased at 6 hours. In another model using younger Sprague Dawley rats, at 6 hours there were two different responses. Half the animals demonstrated an EGF-mediated decrease in proinflammatory marker expression while the other half demonstrated increased expression. Together, these data indicate that EGF has both pro-inflammatory and anti-inflammatory effects in vascular tissues. Regardless, (*R*)-DOI inhibited all EGF-induced effects on proinflammatory marker expression. Interestingly, (*R*)-DOI blocked increased proinflammatory marker expression more potently than decreased marker expression. In conclusion, our results indicate that EFG can both be anti- and proinflammatory in vascular tissues, possibly through different mechanisms that are time-dependent. Further, that (*R*)-DOI is more potent at preventing the proinflammatory effects of EGF than the anti-inflammatory effects.

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STRUCTURE-ACTIVITY RELATIONSHIPS OF PSILOCYBIN ANALOGS AT SEROTONIN 5-HT$_2$ RECEPTOR SUBTYPES

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Background: In recent years, many structural analogs of existing hallucinogens have appeared as new designer drugs. While a large amount of experimental work has been conducted to characterize the effects of the tryptamine hallucinogen psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine), there has been little systematic investigation of the structure-activity relationships (SAR) of other 4-substituted tryptamine derivatives. The present investigation attempts to address the gap of information. Methods: SAR studies were conducted with 17 tryptamines containing a variety of *N,N*-dialkyl substituents (methyl, ethyl, propyl, isopropyl, or allyl) and either a 4-hydroxy or a 4-acetoxy group. The ability of these compounds to activate human 5-HT$_2$ subtypes (5-HT$_{2A}$, 5-HT$_{2B}$ and 5-HT$_{2C}$) was assessed using calcium mobilization assays. Head twitch response (HTR) studies were conducted in C57BL/6J mice to assess activation of the 5-HT$_{2A}$ receptor (the site primarily responsible for hallucinogenesis) *in vivo*. The HTR was detected using a head-mounted neodymium magnet and a magnetometor coil; compounds were injected IP and head twitch counts were assessed over 30 min. Results: The tryptamines acted as full or partial agonists at 5-HT$_2$ subtypes. Although the compounds displayed approximately equal potency at 5-HT$_{2A}$ and 5-HT$_{2B}$ sites, they typically had >10-fold lower potency at 5-HT$_{2C}$ sites. In addition, *O*-acetylation reduced the 5-HT$_{2A}$ agonist potency of 4-hydroxylated tryptamines by about an order of magnitude. All of the compounds induced head twitches in mice, consistent with an LSD-like behavioral profile. Most of the compounds had about the same potency as psilocybin (ED$_{50}$ = 1.40 μmol/kg IP) in the HTR assay, indicating that the specific *N,N*-dialkyl substitution pattern is not a major determinant of behavioral potency in mice. Furthermore, in contrast to the *in vitro* data, *O*-acetylation of the 4-hydroxy group had little effect on HTR potency. Conclusions: These findings shed light on the SAR of *N,N*-dialkyltryptamines containing a 4-oxygenated substituent. The tryptamine derivatives have psilocybin-like pharmacological properties, supporting their classification as serotonergic hallucinogens. Psilocybin is rapidly *O*-dephosphorylated to psilocin (4-hydroxy-*N,N*-dimethyltryptamine) *in vivo* and is thought to act as a pro-drug; comparison of the *in vivo* and *in vitro* potencies of the 4-acetoxy-*N,N*-dialkyltryptamines indicates those compounds may also serve as pro-drugs for their *O*-deacetylated derivatives.

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MDMA's prosocial and rewarding effects require distinct neural mechanisms

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The extensively abused recreational drug ± 3,4-methylenedioxymethamphetamine (MDMA), has shown promise as an adjunct to psychotherapy for treatment-resistant disease. MDMA's prosocial effects and demonstrated ability to facilitate positive social interactions are believed to underlie its potential therapeutic efficacy. It is unknown, however, whether the mechanisms underlying its prosocial therapeutic effects and abuse potential are distinct. MDMA has a high affinity interaction with the serotonin transporter (SERT), leading to efflux of serotonin (5-HT) through a reverse-transport mechanism. Recent work in our laboratory suggests that 5-HT release in the nucleus accumbens (NAc) is important for social reward and social preference. We hypothesized that this mechanism could account for MDMA's prosocial effect, but not its rewarding properties, in a mouse model recapitulating the major aspects of MDMA's human effects. Using adult C57/Bl6 mice, we identified a low dose of MDMA that elicited social preference in a 3-chamber assay, but not conditioned place preference or locomotor activation. A higher dose of MDMA produced all three behaviors. Using intracerebral drug microinjection into the NAc, a conditional knockout of SERT, and fluorescence based imaging of neural activity, we find that MDMA's interaction with SERT in the NAc is necessary to account for its prosocial effect, but does not alter its rewarding properties, which depend on dopamine (DA) receptor activation. We further found that MDMA's prosocial effect, and its acute effect on excitatory synaptic transmission onto D1 and D2 medium spiny neurons (MSNs) of the NAc, require 5HTR1b activation. Neither the acute prosocial effect of MDMA nor its effect on synaptic transmission in the NAc were oxytocin receptor dependent. MDMA's prosocial effect was mimicked by d-fenfluramine, a serotonin-releasing compound with no known addictive properties. Unbiased whole-brain neuron activation mapping studies have identified a network of cortical and subcortical structures that are uniquely activated by MDMA in a social setting. Ongoing experiments are exploring whether activating these networks *in vivo* can replicate MDMA's behavioral effects. Our data suggest that the prosocial, therapeutic effects of MDMA could potentially be recreated through a neural circuit-based mechanism that minimizes this drug's abuse potential.
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A single dose of psilocybin, but not ketamine, produces persistent antidepressant-like effects in a rat model of depression.

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Background Psilocybin has recently demonstrated profound efficacy to alleviate depression and anxiety in several clinical trials and has received Breakthrough Status by the FDA. Symptomatic relief after only one or two therapeutic treatments last for at least several months in the vast majority of individuals. The basis for the persistent antidepressant and anxiolytic effects are unknown. One possibility is that the therapeutic effects are psychological, relying upon the subject's personal experience while under the influence of high levels of drug during the peak experience. Subsequent therapy sessions then involve integration of the experience with the goal of reorganizing thought to a healthier baseline state. Another possibility is that the antidepressant effects rely upon neurochemical changes induced by psilocybin that correct abnormalities leading to a healthier brain state. In this scenario, the subjective peak experience would serve as a biomarker that sufficient psilocybin was administered to affect the neurochemical changes.

Methods To distinguish between these possibilities, we used an animal model of depression, Wistar-Kyoto rats, in a series of experiments with single doses of psilocybin, lysergic acid diethylamide (LSD), or ketamine to evaluate the persistence of behavioral differences versus control rats. We used delayed (single) and repeated (weekly) forced swim test, and endpoint elevated plus maze to quantify behaviors correlated to depression and anxiety in the human demographic.

Results/Conclusions Remarkably, we have found that a single treatment with psilocybin produces long lasting and persistent antidepressant-like and/or anxiolytic effects in rats, but that the observed behaviors are dependent upon the rats' experiences during the week after administration. We replicated some of these findings with LSD, but found ketamine's effects both transient and independent of experience. These results indicate that the persistent therapeutic benefits of psychedelics are biological, but expressed within the context of subjective experience, perhaps by facilitating a period of behavioral flexibility following psychedelic experience.

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PSILOCYIBN VS. NICOTINE PATCH: RANDOMIZED COMPARATIVE EFFICACY TRIAL

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Background: We conducted an open-label pilot study testing psilocybin in combination with manualized cognitive behavioral therapy (CBT) in 15 treatment-resistant smokers. Data showed no serious adverse events attributable to psilocybin, and a very promising cotinine-verified point-prevalence abstinence rate of 80% at 6-month follow-up. A 2.5-year follow-up showed a cotinine-verified abstinence rate of 60%.

Methods: We are currently conducting a comparative efficacy trial randomizing treatment-resistant smokers to a single psilocybin session (on their target quit date) or the transdermal nicotine patch (using FDA guidelines, beginning 24 hours after their target quit date), both in combination with a 13 week program of manualized CBT. Before their target quit date (and after 24 hours of temporary nicotine abstinence), participants undergo fMRI, during which they complete the Multi-Source Interference Task (MSIT), a measure of cognitive control. Participants also undergo fMRI and complete the task 24 hours after the target quit date.

Results: Interim results show substantially higher cotinine-verified 12-month abstinence rates with psilocybin (47%, n=15) vs. nicotine patch (n=10, 20%) among those completing the 13-week treatment course. MSIT results show significant pre vs. post target quit date reductions in the reaction time for correct incongruent trials in psilocybin participants (n=17), and no change in the nicotine patch participants (n=10). Psilocybin participants also showed a significant pre vs. post increase in percent correct responses on incongruent trials. Psilocybin also normalized activation in the right lingual gyrus during incongruent trials, with activation for congruent and incongruent trials being similar in the psilocybin group, but incongruent trials showing less activation than congruent trials in the nicotine patch group.

Conclusions: Smoking cessation efficacy analyses suggest promising results for psilocybin in comparison to transdermal nicotine patch when both are delivered in combination with CBT. Moreover, preliminary neurocognitive analyses suggest significantly improved cognitive control and a normalization of fMRI response in the right lingual gyrus the day after quitting for the psilocybin group, suggesting psilocybin may improve smoking cessation outcomes by enhancing cognitive control.

Funding for primary trial provided by Heffter Research Institute, Beckley Foundation, and William Harrison. Funding for fMRI provided by NIDA-IRP.

DIMETHYLTRYPTAMINE INCREASES PROLIFERATION OF HUMAN NEURAL CELLS IN BRAIN ORGANOIDS

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Background: Ayahuasca is a psychedelic brew that shows a rapid and potent antidepressant effect in clinical trials of treatment-resistant depression. However, little is known about the effects of Ayahuasca components on the cellular and molecular levels. In rodents, classical antidepressants reverse the symptoms of depression by stimulating proliferation of neural cells. Here we hypothesize that N,N-dimethyltryptamine (N,N-DMT), the main psychedelic compound found in the Ayahuasca brew, stimulates proliferation of human neural stem cells, which could be associated to the antidepressant effects of the brew.

Methods: Neural stem cells (NSCs) and brain organoids derived from human induced pluripotent stem cells were used to evaluate effects of N,N-DMT. NSCs were treated with N,N-DMT (1uM, 10uM and 30uM) for 24 hours and cell viability and proliferation were measured. Brain organoids were treated with 1uM N,N-DMT for 10 days and immunofluorescence performed for cell cycle markers, Ki67 and phospho-histone H3 (pHH3).

Results and Conclusions: N,N-DMT induced a significant increase in cell proliferation in NSCs, in a dose dependent manner. This effect was also observed in brain organoids, where N,N-DMT induced an increase of about 60% in the amount of Ki67+ cells as well as an increase of about 25% in the size of proliferative areas. Taken together, our results suggest that dimethyltryptamines present in the Ayahuasca brew, control cell proliferation in the neural cells that could explain some of its antidepressant effects.

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Rostral Anterior Cingulate Thickness Predicts the Psilocybin Experience

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Background: Psychedelic research is currently under resurgence with both clinical and non-clinical studies. While "set and setting" influence the subjective experience of psychedelics (e.g. Feeling of Unity, Bliss, Spiritual Experience, and Insightfulness), an intriguing question remains whether biological factors can predict psilocybin-induced states. Past research demonstrates individual brain morphology can predict many aspects of neuronal activity, drug response, and human behavior. Common constructs of the psychedelic experiences are mediated by the serotonin 2A (5-HT2A) receptor, which has high expression in the cingulate cortex compared to other limbic regions. We hypothesized that greater individual cingulate thickness would predict higher subjective ratings in Feeling of Unity, Bliss, Spiritual Experience, and Insightfulness in healthy controls after psilocybin.

Methods: Healthy participants (N = 55; 33M/22F; M_{age}=25yrs (*SD*=3.96) received either placebo or psilocybin (0.160 or 0.215 mg/kg) and underwent structural magnetic resonance imaging (MRI). Participants completed the self-report 5D-ASC questionnaire 360 min after psilocybin and placebo intake, psilocybin minus placebo scores were used for analyses. FreeSurfer was used to calculate rostral anterior, caudal, and posterior cingulate thickness. Multiple regressions controlling for sex, age, and dose were used to assess if brain morphology predicts the psilocybin experience.

Results and Conclusions: We found a significant positive association between right rostral anterior cingulate thickness and all four constructs, and a positive association between the left rostral anterior cingulate thickness and Unity. We found no significant associations with left caudal anterior or posterior cingulate thickness. The anterior cingulate is highly implicated in depression and emotional and self-processing in healthy individuals. We show rostral anterior thickness predicts the potentially therapeutic aspects of psilocybin as demonstrated by psilocybin-assisted therapy trials. Further, our results indicate right hemisphere cingulate morphology is a better predictor compared to the left. These results align well with previous findings from our group and others that classic psychedelic compounds induce hyperfrontal effects particularly in the right hemisphere. Our results highlight the possibility of individual brain morphology serving as a predictive biomarker for the psilocybin experience in healthy controls. This information may be useful for both clinical applications and understanding brain correlates with pharmacologically induced states in healthy individuals.

This study was financially supported with grants from the Heffter Research Institute and the Swiss Neuromatrix Foundation.

ACUTE EFFECTS OF PSILOCYBIN ON GLUTAMATE CONCENTRATION LEVELS, FUNCTIONAL CONNECTIVITY, AND SUBJECTIVE STATE: A PLACEBO-CONTROLLED EXPERIMENTAL STUDY IN HUMANS

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Background: There is growing interest in the therapeutic utility of psychedelic substances, like psilocybin, for increasingly common and difficult to treat disorders like depression. Thus an important question is how these substances act in the brain. Accumulating evidence suggests that classic psychedelics stimulate 5-HT_{2A} receptors located on neocortical pyramidal cells, which is the suggested primary mechanisms of action for the hallucinogenic effect. However, it has also been recognized that, in rodents, psychedelics elevate levels of cortical glutamate, which has been implicated in the acute actions of the substances on brain function and behavior. To our knowledge, no study has yet investigated the acute effect of a psychedelic on brain glutamate levels in humans. Therefore, the aim of the present study was to assess the acute influence of psilocybin on brain glutamate levels in the medial prefrontal cortex (mPFC) and hippocampus. Additionally, as glutamate release has been implicated in acute effects of the drug, we aimed to assess the relationship between glutamate levels, and brain and behavioral outcomes previously found to be affected by psychedelics, including disrupted within and between- network functional connectivity (FC) and well-known subjective effects.

Methods: The present study employed a randomized, placebo-controlled, double-blind, parallel group design. Sixty healthy participants were allocated to a treatment condition (.17 mg/kg psilocybin or placebo). All participants underwent single-voxel proton magnetic resonance spectroscopy and resting state fMRI 60 minutes after treatment administration. Participants also completed the 5-DASC questionnaire at the end of the testing day.

Results and Conclusions: Psilocybin acutely increased glutamate levels in the mPFC, and decreased glutamate levels in the hippocampus. FC alterations were consistent with previous psychedelic imaging results. Alterations in metabolite levels were correlated with changes in subjective state. Metabolite and FC correlation analysis is ongoing and further results will be presented. Preliminary results suggest that glutamate may play an important role in the effects of psilocybin on brain and behavior.
Study was partially funded by the Beckley foundation.

Psychedelic Superagonism and Functional Selectivity Profiling at the Serotonin Receptors

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Background:
Lysergic acid diethylamide (LSD) demonstrates extraordinary potency in humans, but clues to this potency and psychedelic action are found at the receptor signaling level. Previous evidence has shown that LSD can manifest functional selectivity and β-arrestin recruitment *superagonism* at the 5-HT_{2A} receptor, but LSD has not been comprehensively profiled for functional selectivity at other serotonin receptors. This study compares the signaling profile of LSD and a potent N^6-ethyl analog (Eth-LAD) to non-psychedelic ergoline analogs, 2-Br LSD (BOL-148) and lisuride for the purpose of understanding receptor determinants of biased superagonism.
Methods:
Profiles of cellular signaling comparing LSD to Eth-LAD, 2-Br LSD, and lisuride were performed at all 12 human serotonin G protein-coupled receptors (GPCRs) as well as at some dopamine and adrenergic GPCRs. Ligands were profiled by measuring canonical and non-canonical G protein couplings by bioluminescent resonance energy transfer (BRET) techniques, second messenger signaling via luminescence and fluorescence-based assays, real-time internalization/β-arrestin recruitment assays, and kinetic binding assays. Compounds were also further assessed in vivo using an automated rodent head-twitch response (HTR) behavioral assay.
Results and Conclusions:
Distinct signaling patterns emerged demonstrating that Eth-LAD shows superior biased superagonism at many GPCRs. Furthermore, compared to LSD, non-psychedelic 2-Br LSD/lisuride ergolines also show key differences in G protein versus β-arrestin recruitment kinetics. Interestingly, this study reveals what appears to be *key rank orders of potency and signaling bias* across the serotonin receptors, likely to be predictive of in vivo psychedelic activity. This study reveals important determinants of biased superagonism and potential therapeutic avenues of treatment for the psychedelic drug class.

Study funded by pilot grants from Research Affairs Council and start-up funds at Medical College of Wisconsin

5-HT_{2A} RECEPTOR AGONISTS AS ANTI-INFLAMMATORY THERAPEUTICS

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Background: Activation of serotonin 5-HT_{2A} receptors with what are typically regarded as psychedelics produces profound and potent anti-inflammatory effects in several models. These include cellular-based and whole animal systems where receptor activation potently blocks the effects of TNF-a. Additional recent work has established that 5-HT_{2A} receptor activation also blocks inflammation induced by epidermal Growth Factor (EGF) in cell-based and ex-vivo systems. Studies in rodent models of the human inflammatory disease asthma have shown that several, but not all, agonists at 5-HT_{2A} receptors have potent effects to prevent the development of inflammation and its physiological consequences associated with allergic asthma. These results indicate functionally selective mechanisms for recruitment of anti-inflammatory pathways to the receptor by different ligands. These anti-inflammatory pathways do not correlate with either calcium mobilization, a measure of Ga-q activity, or b-arrestin recruitment. More recently, we have demonstrated that the 5-HT_{2A} receptor agonist (*R*)-DOI has anti-inflammatory effects in a mouse model of metabolic and cardiovascular disease, and has the ability to prevent and reverse inflammation and lung fibrosis associated with pre-existing asthma symptoms in a new model of chronic asthma.

Methods: Metabolic and cardiovascular disease was modeled in the high fat-fed ApoE -/- mouse model, which develops vascular inflammation and metabolic disease upon feeding a high fat “Western” diet. To assess the effects of 5-HT_{2A} receptor activation, (*R*)-DOI was implanted subcutaneously to release low levels of drug over the 16 weeks of high fat feeding. Outcome measures included expression of proinflammatory marker genes from vascular tissue, fasting blood glucose levels, and measures of circulating cholesterol. To determine the effects of (R)-DOI on pre-existing asthma, we developed a new paradigm of OVA exposure that produces inflammation, airways hyperresponsiveness, and fibrosis that is stable for at least two weeks after the final ovalbumin exposure. (R)-DOI was administered nose-only one per day for four days beginning one week after the final OVA exposure.

Results and Conclusions: Continuous release of low levels of (*R*)-DOI in high fat-fed ApoE -/- mice reduced vascular inflammation, normalized blood glucose levels, and lowered total circulating cholesterol. Treatment of mice with pre-existing asthma with nose-only (*R*)-DOI normalized airways hyper-responsiveness to baseline levels, normalized pulmonary inflammation to near baseline levels, and significantly reversed and normalized collagen deposition and lung fibroses. These results extend previous findings regarding the potential of 5-HT_{2A} receptor agonist-based therapeutic strategies to treat inflammatory diseases. Importantly, our data indicate that this strategy can treat pre-existing asthma with disease-modifying effects, as well as treat cardiovascular and metabolic disease, which together affect large percentages of the population.

PSYCHEDELICS AS INSPIRATION FOR PLASTICITY-PROMOTING NEUROTHERAPEUTICS

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Background: The prefrontal cortex plays a key role in the regulation of mood, fear, and reward. Atrophy of neurons in this critical brain region is a hallmark of depression and related neuropsychiatric diseases. Therefore, strategies capable of increasing the growth of neurons in the prefrontal cortex have enormous therapeutic potential. Known as psychoplastogens, small molecules capable of rapidly promoting neural plasticity are now being recognized for their ability to repair damaged neural circuitry. Ketamine—the prototypical psychoplastogen—was recently approved by the FDA for treatment-resistant depression. However, until recently, relatively few psychoplastogens had been identified.

Methods: Using a combination of cellular and behavioral assays, we sought to determine whether or not serotonergic psychedelics might serve as psychoplastogens capable of modifying neural circuitry in rodents relevant to mood and fear memory. Additionally, we were interested in understanding if the hallucinogenic effects of these compounds were necessary for their therapeutic effects. To address this latter question, we took two approaches. First, we treated male and female rats with sub-hallucinogenic doses of the psychedelic *N,N*-dimethyltryptamine (DMT) on a chronic, intermittent schedule to mimic psychedelic microdosing in humans. Next, we engineered analogs of DMT and ibogaine lacking hallucinogenic effects, and tested them in cellular models of neural plasticity as well as mouse behavioral tests relevant to depression and post-traumatic stress disorder (PTSD).

Results and Conclusions: We found that psychedelic compounds promote structural and functional neural plasticity, which may explain their therapeutic effects in the clinic. Moreover, the hallucinogenic properties of psychedelics do not appear to be necessary for their effects on plasticity or several rodent behaviors relevant to depression and post-traumatic stress disorder. These results have important implications for the development of next-generation neurotherapeutics.

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LYSERGIC ACID DIETHYLAMIDE REGULATES SYNAPTIC PROTEINS IN HUMAN BRAIN ORGANOIDS

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Background: Lysergic acid diethylamide (LSD), considered the prototypical psychedelic molecule, has effects on consciousness and perception. However, the molecular mechanisms involved in LSD effects in humans and how it may be translated into changes in physiology are still poorly understood. Here we used cerebral organoids as a biological live model to explore LSD effects in human brain cells. Mass spectrometry-based proteomics were performed to gain insights on molecular targets and signaling pathways involved in the mid and long-term effects of LSD.

Methods: Brain organoids derived from human induced pluripotent stem cells were treated with 10nM LSD for 1 or 4 days. Proteomic analyzes were performed by 2D-Liquid chromatography–mass spectrometry (LC-MS) system and further analyzed through String and Gene Ontology (GO) software. Immunohistochemistry was performed to assess structural and morphological integrity of the brain tissue as well as to validate proteomic data.

Results and Conclusions: Control and LSD-treated brain organoids exhibited similar patterns of cellular organization. Proliferative areas, also called ventricular zones, were positive for nestin, a maker of neural stem cells and progenitor cells. MAP2, a neuron-specific cytoskeletal protein, was preferentially located in the cortical layers and surrounding ventricular zones in both control and treated brain organoids. LC-MS based proteomics identified 3448 proteins with a total of 234 proteins significantly regulated by LSD ($p<0.05$). GO analysis showed 'presynaptic active zone' as one of the significantly enriched terms ($p= 0,005$; $q<0.2$). Within this category, synaptophysin (SYP), a major integral membrane protein ubiquitously expressed in synapses was shown to be upregulated (fold change = 4.92 ± 1.69). Immunofluorescence for SYP revealed that it was mainly expressed in the cortical area of brain organoids. LSD treatment for 4 days induced a more than 2-fold increase in the levels of SYP in cortical plate-like regions of the human brain organoids. Taken together these results suggest LSD stimulates human neurons to increase the expression of synaptophysin, thus becoming more prone to form synapses, an essential event for neural plasticity and reorganization.

Study funded by Beckley Foundation, FAPERJ, CNPq/CAPES Decit/SCTIE/MoH and IDOR/Rede D'Or Hospitals Network.

SUBACUTE EFFECTS OF THE PSYCHEDELIC AYAHUASCA ON THE SALIENCE NETWORK RELATE TO INCREASED SOMESTHESIA AND AFFECT

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Background: Recent years have seen a growing interest in the therapeutic use of psychedelic for the treatment of anxiety and depression in patients with affective and mood disorders. Neuroimaging studies have just begun to explore how brain networks supporting perceptual and higher-order cognitive functions are affected during the acute effects of psychedelics. Even less is known on the neural basis of the subacute effects taking place one to a few days after the psychedelic experience. This study focused on the subacute changes of a single session with the psychedelic ayahuasca over the salience network, a distributed brain network that underlies homeostatic behavioral guidance supporting socioemotional functions.
Methods: We leveraged task-free functional magnetic resonance imaging data one day before and one day after a randomized placebo-controlled experiment exploring the effects of ayahuasca in naïve healthy participants (21 placebo/22 ayahuasca). We derived functional connectivity maps of the salience network using a seed-to-whole brain approach, and statistically assessed post-session functional connectivity changes between the ayahuasca and placebo groups.
Results: Our findings revealed increased functional connectivity in the anterior cingulate cortex, a key node of the salience network, one day after the session in the ayahuasca group. Increased connectivity of the anterior cingulate cortex correlated positively with changes in somesthesia and affect perceived during the acute effects of ayahuasca.
Conclusion: These findings provide preliminary evidence for subacute functional changes induced by a psychedelic substance in the salience network, a socioemotional relevant neural system known to be involved in affective processes and interoception.
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Psilocybin induces time-dependent changes in global brain connectivity

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Background: The use of Psilocybin in scientific and experimental clinical contexts has triggered renewed interest in the mechanism of action of psychedelics. However, its time-dependent systems-level neurobiology remains sparsely investigated in humans.

Methods: We therefore conducted a double-blind, randomized, counterbalanced, cross-over study during which 23 healthy human participants received placebo and 0.2 mg/kg of psilocybin p.o. on two different test days. Participants underwent MRI scanning at three time points between administration and peak effects: 20 mins, 40 mins, and 70 mins after administration. We quantified resting-state functional connectivity via a data-driven global brain connectivity method and compared it to cortical gene expression maps.

Results: Psilocybin reduced associative, but concurrently increased sensory brain-wide connectivity. This pattern emerged over time from administration to peak-effects. Furthermore, we show that baseline connectivity is associated with the extent of Psilocybin-induced changes in functional connectivity. Lastly, Psilocybin-induced changes correlated time-dependently with spatial gene expression patterns of the 5-HTR2A and 5-HTR1A.

Conclusion: Together, these results suggest that the integration of sensory and the dis-integration of associative regions may underlie the psychedelic state and pinpoint the critical role of the serotonin 2A and 1A receptor systems. Furthermore, baseline connectivity may represent a predictive marker of the magnitude of changes induced by psilocybin and may therefore contribute to a personalized medicine approach within the potential framework of psychedelic treatment.

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Naturalistic studies on the impact of 5-MeO-DMT on health parameters and neuroendocrine markers

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5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) is a psychedelic substance found in the secretion from the parotoid glands of the Bufo alvarius toad. Inhalation of vapor from toad secretion containing 5-MeO-DMT has become popular in naturalistic settings as a treatment of mental health problems or as a means for spiritual exploration. However, knowledge of the effects of 5-MeO-DMT in humans is limited. Data from 2 naturalistic studies are presented. The aim of the first study was to assess sub-acute and long-term effects of inhaling vapor from dried toad secretion containing 5-MeO-DMT on affect and cognition. Assessments at baseline, within 24 h and 4 weeks following intake, were made in 42 individuals who inhaled vapor from dried toad secretion at several European locations. The aim of the second study was to assess the effects of inhalation of vaporized synthetic 5-methoxy-N,N-dimethyltryptamine on neuroendocrine markers and mental health parameters. Assessments (baseline, immediately post-session, and 7-days follow-up) were made in 11 participants. Salivary samples were collected at baseline and post-session and analyzed by high-sensitivity enzyme-linked immunosorbent assay (ELISA). Relative to baseline, ratings of satisfaction with life and convergent thinking significantly increased right after intake and were maintained at follow-up 4 weeks later. In the first study, ratings of mindfulness also increased over time and reached statistical significance at 4 weeks. Ratings of depression, anxiety, and stress decreased after the session, and reached significance at 4 weeks. Participants that experienced high levels of ego dissolution or oceanic boundlessness during the session displayed higher ratings of satisfaction with life and lower ratings of depression and stress. In the 2nd study, 5-MeO-DMT significantly increased cortisol levels and decreased IL-6 concentrations in saliva immediately post-session. Relative to baseline, ratings of non-judgement significantly increased, and ratings of depression decreased immediately post-session and at follow-up. Ratings of anxiety and stress decreased from baseline to 7-day follow-up. Inhalation of vaporized 5-MeO-DMT produced significant changes in inflammatory markers and improved mental health parameters in volunteers. These results warrant exploratory research into therapeutic applications of 5-MeO-DMT.

BIOLOGICAL EFFECTS OF β-CARBOLINES AND SEROTONERGIC PSYCHEDELICS IN HUMAN NEURAL CELLS AND BRAIN ORGANOIDS

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Background: In the last few years, progress has been made regarding the differentiation of human induced pluripotent stem (iPS) cells into neural cells and brain organoids. These approaches recreate features of the cerebral cortex development, showing potential for human brain modeling studies. Here, I will present our recent data regarding the effects of the β-carboline alkaloid harmine, N,N-dimethyltryptamine (NN-DMT), 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) and LSD (lysergic acid diethylamide) in live human neural tissues.

Methods and Results: Harmine increased the pool of neural progenitor cells by inhibiting DYRK1A (dual specificity tyrosine-phosphorylation-regulated kinase). NN-DMT increased the number of neural stem cells, in a dose dependent manner, through the activation of 5HT2A receptor. These results suggest that harmine and NN-DMT influence neurogenesis, which is probably associated with the antidepressant effects of Ayahuasca described in patients. Human neurons exposed to NN-DMT also showed increased expression of synaptophysin, similar to BDNF (brain derived neurotrophic factor), while analyses of brain organoids exposed to 5-MeO-DMT revealed proteins broadly distributed on functional activities such as cellular protrusion formation, microtubule dynamics and cytoskeletal reorganization. Liquid chromatography mass spectrometry based-proteomics identified 235 proteins in human brain organoids which significantly changed expression after exposure to LSD. An enrichment in “presynaptic active zone” proteins was revealed. LSD induced a 2-fold increase in the levels of synaptophysin in the cortical plate-like region of brain organoids.

Conclusions: These data contribute to elucidate neuroplasticity signaling pathways induced by β-carbolines and serotonergic psychedelics and suggest that both dimethyltryptamines and LSD stimulate neurons to become prone to form new synapses. Human iPS cells offer an exciting new range of opportunities to investigate the influence of psychedelics in the central nervous system.

Study funded by Beckley Foundation, FAPERJ, CNPq/CAPES Decit/SCTIE/MoH and IDOR/Rede D’Or Hospitals Network.

SEROTONERGIC PSYCHEDELICS AS COGNITIVE ENHANCER: POTENTIAL MECHANISMS

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Background: Serotonergic psychedelics produce major psychological changes, both acutely as well as long term. The fact that these substances induce neural plasticity (Dakic et al., 2017, Lima da Cruz et al., 2018 , Ly et al., 2018) suggests their use as cognitive enhancers. Indeed, serotonergic psychedelics can improve memory consolidation when administered after fear learning or object recognition task (ORT) (Zhang et al., 2013, Buchborn et al., 2014). Yet, little is known about the mechanisms underlying these effects. We set out to assess whether psychedelic treatment before ORT would increase learning in rats. To identify underlying mechanisms, we also investigated acute neurophysiological changes in hippocampus (HP) and prefrontal cortex (PFC).
Methods: Wistar rats in different age groups - young (2 months), adults (9 months) and old (12-18 months) - were treated with d-lysergic acid diethylamide (d-LSD), and tested on ORT after a 6-day interval without treatment. In addition, old rats were injected with saline or d-LSD, and exposed to an enriched environment (EE) for 6 days between the last injection and ORT. A separate group of rats was surgically implanted with multi-electrode arrays in the HP and PFC, and a cannula in the third ventricle for the injection of d-LSD or 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT). Local field potentials (LFP) recorded with an Intan RHD2000, behavior recorded with a Plexon system, and data analyzed using Matlab.
Results and Conclusions: d-LSD treatment led to significantly better ORT performance in young and adult rats, while old rats required d-LSD treatment followed by EE exposure in order to prefer novelty. The acute effects of d-LSD and 5-MeO-DMT included a decrease of LFP power in the low gamma band (20-50 Hz) in both HP and PFC, with a corresponding power increase in the delta band (0-5 Hz). These electrophysiological changes mimic the spectral profile of slow-wave sleep (SWS), despite the fact that the rats were awake. Given SWS-induced synaptogenesis (Yang et al., 2014), the results suggest that d-LSD produces acute electrophysiological changes that promote synaptogenesis, which in the long-term modify the synaptic landscape so that it grows more apt to learn from new stimuli.

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EFFECTS OF N,N-DMT ON HUMAN ASTROCYTES: IMPLICATION FOR SYNAPTOGENESIS

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Background: Psychedelics acts mainly on the serotonergic system, capable of altering perception and consciousness. N,N-dimethyltryptamine (N,N-DMT) is a naturally occurring psychoactive indole present in *Psychotria viridis* leaves, used in many cultures as part of mystic-religious rituals through the ingestion of Ayahuasca brew. Psychedelics have been explored as potential therapeutic agents to treat conditions such as depression, improving mental and physical health. However, there is limited understanding of its effects at the cellular level. As a nervous system modulator, N,N-DMT probably affects neurons as well as astrocytes, the largest cell population in the brain. Astrocytes are crucial for homeostasis and can directly regulate many features impaired in depressive disorders, including neuronal survival and synaptic plasticity. The aim of this study is to investigate the effects of N,N-DMT on human astrocytes *in vitro*.
Methods: Skin fibroblasts were reprogrammed to obtain human induced pluripotent stem (iPS) cells. These cells undergone differentiation to astrocytes. Cell phenotypes were characterized by PCR and immunostaining. Astrocytes were exposed to N,N-DMT (1µM, 10 µM and 100 µM) for 72h to assess cell viability. Lysates of astrocytes treated with N,N-DMT (10µM) for 24h were obtained to determine the relative expression of neurotrophins and astroglial pre- and post-synaptic modulators.
Results and conclusion: Human iPS-derived astrocytes express the main astroglial markers, such as GFAP, Vimentin, s100β, ALDH1L1, EAAT1 and EAAT2. mRNA for serotonin receptors and the non-opioid receptor sigma 1 were also detected in the astrocytes. Exposure to N,N-DMT did not alter cell viability. N,N-DMT increased the expression of Glypican 4, one of the main synaptogenic molecules secreted by astrocytes that exerts its effects on the post-synaptic terminals. Our results show that this psychedelic compound affects directly human glial cells, suggesting a mechanism related to synaptic plasticity via astrocytes that could explain some of its therapeutic effects.

Study funded by FAPERJ, CNPq/CAPES Decit/SCTIE/MoH and IDOR/Rede D'Or Hospitals Network.

SYNTHESIS AND BIOLOGICAL EVALUATION OF TRYPTAMINES FOUND IN HALLUCINOGENIC MUSHROOMS: NORBAEOCYSTIN, BAEOCYSTIN, NORPSILOCIN AND AERUGINASCIN

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Background: Individuals experienced with the use of psychedelics have often shared anecdotal reports of variability in effects when consuming different species of psilocybin mushrooms with assumed varying levels of the structurally related tryptamines baeocystin, norpsilocin, and/or aeruginascin. Additionally, several online reports have claimed that the consumption of specific psychedelic mushrooms have produced temporary muscle weakness or paralysis. The speculations are however largely unsubstantiated, and few scientific studies have been conducted to evaluate pharmacological activity of these tryptamines, largely due to their lack of availability in pure form.

Methods: A general synthetic method was developed to access known tryptamine natural products present in psilocybin-producing mushrooms. *In vitro* and *in vivo* experiments were then conducted to inform speculations on the biological activities (or lack thereof) for the natural products.

Results and Conclusions: The synthetic method was highlighted by an operationally simple and novel approach to the isolation of useful amounts of zwitterionic target compounds. In the mouse head-twitch response (HTR) assay, psychedelic activity by baeocystin alone was not evident despite its putative dephosphorylated metabolite, norpsilocin, possessing potent agonist activity at the 5-HT2A receptor with regard to intracellular calcium mobilization. Furthermore, mice treated with aeruginascin at doses up to 30 mg/kg showed little-to-no evidence of muscle weakness or ataxia. The initial results do not support the hypothesis that the known minor tryptamines found in psychedelic mushrooms contribute significantly to the psychedelic experience.

Poster Presentations

Abstracts are listed alphabetically by presenting author.

Empirically identified benefits and challenges of LSD and psilocybin microdosing

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Background: Psychedelic microdosing is the practice of consuming low, sub-hallucinogenic doses of psychedelic substances, such as lysergic acid diethylamide (LSD) or psilocybin-containing mushrooms. Doses are typically 1/10th of a regular recreational dose. The scientific literature contains very limited research on this practice, which has led to rampant speculation.

Methods: Our research addresses the fact that barely any research has reported on adverse effects associated with microdosing. Additionally, our research identifies actionable research foci where microdosing shows the most potential. By quantifying reports from a sample of 278 LSD and psilocybin microdosers we describe high potential research avenues and areas of concern.

Results and Conclusions: Beneficial possibilities include improved mood, focus, creativity, and self-efficacy. Areas of concern include illegality-related concerns, physiological discomfort, impaired focus, and increased anxiety. Of important note are the parallels between benefits and challenges that help provide high-potential research avenues. For example, several participants report cognitive enhancement, but several also report impaired cognition; contrast this with the many participants reporting improved mood versus the relatively few reporting mood impairments. This suggests that mood interventions may be more promising than cognitive enhancement for microdosing research. Leveraging such participant reports distills the highest-potential intervention targets so research funding can be efficiently allocated. This mixed-methods study resulted in a structured research plan for a phase IIa clinical trial of psilocybin microdosing planned to begin in Toronto, Canada in early 2020. Microdosing research complements regular-dose research and provides an opportunity to challenge theories about mechanisms of clinical change predicated on the phenomenology of the psychedelic experience. It may be that neuropharmacological mechanisms play a role that microdosing can help elucidate. This framework informs researchers and clinicians as proper experimental microdosing research begins in earnest.

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Note: This abstract is based on research that was recently published with the following citation:
Anderson, T., Petranker, R., Christopher, A., Rosenbaum, D., Weissman, C., Dinh-Williams, L.-A., Hui, K., Hapke, E. (2019). Psychedelic microdosing benefits and challenges: An empirical codebook. Harm Reduction Journal, 16(1), 43. https://doi.org/10.1186/s12954-019-0308-4

Selective Agonism of the 5HT2A Receptor Suppresses Profibrotic Gene Expression and Fibroblast to Myofibroblasts Trans-differentiation.

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Background: Fibrosis, a deleterious consequence of chronic inflammatory diseases, is characterized by the trans-differentiation of fibroblasts into myofibroblasts and their subsequent uncontrolled production of Smooth Muscle Actin (SMA) and collagen fibers. Over time, these processes eventually destroy tissue integrity and function leading to organ failure. While the effect of serotonin is well-defined in the brain, the extensive role of peripheral serotonin (5HT) in disease-promoting inflammation and fibrosis is only currently being established. Recently, it was demonstrated that serotonin incited fibrosis through agonism of the 5HT2B receptor; whereas, antagonism of the 5HT2A receptor (5HT2AR) by ketanserin resolved the fibrotic phenotype. In contrast, our lab and our colleagues have observed that in both ocular and pulmonary disease models, treatment with specific 5HT2AR agonists, like R-DOI, reduced the generation of fibrotic lesions. We hypothesize that these contradictory findings might be due to promiscuous agonist/antagonist ligands obfuscating the individual roles of 5HT2Rs or effecting other receptor classes.
Methods & Results: To determine if the 5HT2AR agonist, R-DOI, either inhibited or promoted fibrosis, we assessed its direct effects on key processes associated with fibrosis. Quantitative PCR and multiplex arrays revealed reduced expression of essential profibrotic cytokines including, TGF-β, IL-6, -4, and -10. TGF-β, the main inducer of fibrosis, mediates activation of SMAD signaling pathways, which result in the expression of key fibrotic genes. In a promoter-reporter assay, R-DOI inhibited SMAD pathway activation, as well as downstream gene expression of COL1A1, COL1A2, and ACTA2. Additionally, slot blot analysis confirmed that the R-DOI-mediated decrease in COL1A1 RNA expression correlated with a decrease in collagen protein. Finally, a high-throughput immunofluorescent assay was devised to assess fibroblast trans-differentiation to myofibroblasts via expression of the biomarker, SMA. R-DOI treatment inhibited fibroblast trans-differentiation to the disease-promoting myofibroblast phenotype. R-DOI co-treatment with a 5HT2AR antagonist, MDL100907, reversed R-DOI's anti-fibrotic effects.
Conclusions: R-DOI, a 5HT2AR agonist was shown to reduce fibrotic processes including: production of pro-fibrotic cytokines; fibroblast-associated profibrotic gene expression; SMA and collagen fiber production; and fibroblast to myofibroblast trans-differentiation. Altogether, these results indicate that 5HT2AR agonists, like R-DOI, may have broad acting therapeutic applicability in the prevention of fibrosis-associated diseases.

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Elucidating Anti-Inflammatory SAR at the 5-HT_{2A} Receptor

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Given the recent resurgence of clinical interest in the application of classical serotonergic psychedelics as treatment for various disease states (e.g., end-of-life anxiety, treatment-resistant depression, substance use disorders, obsessive compulsive disorder), a comprehensive analysis of the structure-activity relationship (SAR) is necessary to fully understand the differential expression of behavioral and physiological effects elicited by these compounds. While the field is mostly focused on action within the central nervous system, previously published data from our laboratory supports the use of serotonin (5-hydroxytryptamine; 5-HT) 2A receptor (5-HT_{2A}R) agonists as potent modulators of tumor necrosis factor (TNF)-α-mediated inflammatory processes in the periphery. This emerging therapeutic area holds significant promise for treating peripheral inflammatory disorders, such as atherosclerosis, allergic asthma, and inflammatory bowel syndrome. Whereas whole organism models will provide insight into the physiological response profile, the mechanism of action and structural basis mediating the anti-inflammatory activity have yet to be elucidated on a molecular level.
We hypothesize that a distinct signaling pathway triggered by 5-HT_{2A}R activation mediates the anti-inflammatory response to these ligands. In this study, we analyzed a comprehensive panel of 5HT_{2A}R ligands comprising four chemical classes: tryptamines, ergolines, phenethylamines, and phenisopropylamines. Initial results from examination of the canonical $G\alpha_q$ pathway (using a calcium mobilization measure) and recruitment of the multi-adaptor protein β-Arrestin2 (using a luciferase reporter gene assay) exhibited no significant correlation between potency and efficacy for either pathway with *in vivo* measures of anti-inflammatory activity. Ongoing studies are examining additional GPCR-mediated signaling ($G_{i/o}$, G_s) via a BRET-based association assay. With this data, the varying degree of effector pathway bias can be determined for each ligand which supports better understanding of adverse and favorable therapeutic activities, as well as informs structure-activity studies and drug candidate selection matrices. The collective analysis of a comprehensive panel of 5HT_{2A}R ligands has never been examined in this fashion; thus, we aim to elucidate the SAR to inform drug design for novel molecules that are biased to pathways targeting a biologically therapeutic response.

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Exploring 5-HT_2 Receptors as Targets for Treating Epilepsy in Fragile X Syndrome: A Preclinical Study of *Fmr1* Knockout Mice

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Recent clinical data report that the 5-HT_2 agonist, lorcaserin, and the serotonin (5-HT) releaser, fenfluramine, abate seizures in children with Dravet and Lennox-Gastaut syndromes. Evidence suggests their neuropharmacotherapeutic effects, e.g., anorexigenic, are dependent on 5-HT_{2C} receptor activation. At high doses, however, lorcaserin and the metabolite of fenfluramine, norfenfluramine, also activate 5-HT_{2A} receptors, and both drugs can produce psychedelic effects. The present experiments were designed to evaluate the efficacy and possible 5-HT_{2A} and/or 5-HT_{2C} receptor mechanism(s) of lorcaserin to treat audiogenic seizures in young (P23–P26), *Fmr1* knockout mice, a genetic model useful for studying fragile X syndrome (FXS). FXS is a monogenetic, neurodevelopmental disorder characterized by cognitive disabilities, severe anxiety, autism, and sensory hypersensitivities. Up to 20% of people with FXS also have epilepsy, and audiogenic seizures in *Fmr1* knockout mice closely model seizures in FXS that can be triggered by excessive sensory stimulation.
Male and female, wild-type and *Fmr1* knockout mice (FVB and C57BL/6J) are treated with vehicle, 1 mg/kg lorcaserin, a dose that activates 5-HT_{2C} receptors in rodents, or 3 mg/kg, a dose that activates 5-HT_{2A} and 5-HT_{2C} receptors, and 30 min later are exposed to a 120-dB alarm for five consecutive minutes. Separate groups are pre-treated with M100907 (0.03 mg/kg) or SB242084 (0.3 mg/kg) to discern contributions of 5-HT_{2A} or 5-HT_{2C} receptors, respectively. Scored behaviors include wild-running and jumping, tonic-clonic seizures with full recovery, and tonic-clonic seizures progressing to respiratory arrest. Immediately after testing, vehicle-treated wild-type and *Fmr1* knockout mice are euthanized, brains are extracted, and membranes are collected for saturation binding experiments to determine binding site densities of 5-HT_{2A} and 5-HT_{2C} receptors using [^{3}H]Ketanserin and [^{3}H]Mesulergine, respectively. Preliminary results suggest both doses of lorcaserin are prophylactic for audiogenic seizures in *Fmr1* knockout mice. One mouse (1/11) treated with lorcaserin displayed a tonic-clonic seizure and recovered fully. None of the other lorcaserin-treated mice exhibited any seizure-like behavior (N=7, 3 mg/kg; N=3, 1 mg/kg), while 38% (3/8) of vehicle-treated *Fmr1* knockout mice tested thus far exhibited tonic-clonic seizures. Results from this study could guide repurposing of 5-HT_2 agonists to treat seizures in FXS.

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Synthesis and structure activity relationships of novel 4-phenyl-2-dimethylaminotetralins at the 5-HT_{2A} G-protein coupled receptor

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An imbalance of serotonergic signaling in the central nervous system is associated with symptoms of depression, schizophrenia, and substance use disorders, making 5-HT receptors an attractive pharmacotherapeutic target for several neuropsychiatric indications. Indeed, numerous studies have suggested that inactivation of 5-HT_{2A} G-protein coupled receptors (GPCRs) contribute to the improved antipsychotic efficacy of so-called second-generation antipsychotic drugs towards negative symptoms of schizophrenia and may also be a useful medication development strategy for substance use disorder. This presentation reports the synthesis and structure–activity relationships (SAR) of a series of novel 4-phenyl-2-dimethylaminotetralin (4-PAT) derivatives. SAR were derived from affinity and functional assays, in addition to the results of behavioral studies in mouse models of psychosis and *in vivo* pharmacological analysis in non-human primates (NHP). Experimental findings indicate that 4-PATs bind stereoselectively to 5-HT_{2A} receptors with modest to high selectivity over homologous 5-HT_{2B} (>500-fold) and 5-HT_{2C} (>100-fold) GPCRs. Introduction of aryl substituents at the C(4)-phenyl meta position affords high affinity 5-HT_{2A} ligands (<1 nM) for both *cis*- and *trans*-diastereomers, though selectivity over 5-$HT_{2B/C}$ receptors is best observed in the *cis*-configuration. Functional assays measuring hydrolysis products of the primary second messenger inositol triphosphate indicate 4-PATs inactivate 5-HT_{2A} signaling (inverse agonism) with similar potency and efficacy as the recently approved antipsychotic pimavanserin (primarily a 5-$HT_{2A/2C}$ inverse agonist), however, certain 4-PATs demonstrate neutral antagonism or partial agonism. The *in vitro* findings are consistent with *in vivo* results showing that 4-PATs potently attenuate the 5-HT_{2A} mediated 2,5-dimethoxy-4-iodoamphetamine (DOI)-elicited head twitch response in mice with potencies that directly correlate with 4-PAT 5-HT_{2A} affinity. Furthermore, a *trans*-4-PAT analog displaying potent 5-HT_{2A} antagonist and 5-HT_{2C} agonist activity *in vitro* does not produce DOI-like discriminative stimulus effects in NHP, but rather antagonizes the discriminative stimulus effects of DOI as evidenced by a rightward shift in the DOI dose-effect function when administered in combination. *In silico* homology modeling and ligand docking experiments are in progress to further elucidate 4-PAT–5-HT_{2A} molecular determinants for affinity and function, and results will be used to inform the design of novel pharmacotherapies for neuropsychiatric indications.

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A SINGLE DOSE OF d-LSD CAN IMPROVE LEARNING IN YOUNG AND ADULT RATS, WHILE OLD RATS REQUIRE d-LSD PLUS EXPOSURE TO ENRICHED ENVIRONMENT

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Background: Learning and memory decay with aging, in correlation with loss of synapses and decreased plasticity. Exposure to an enriched environment (EE) enhances learning & memory in aging rodents. Previous studies have shown that serotonergic psychedelics promote synaptic plasticity and can cause changes in brain function that persist long after the acute effects. We set out to assess whether different protocols of administration of the serotonergic agonist d-lysergic acid diethylamide (d-LSD) can modulate learning in rats of different ages.

Methods: Young (2 months), adult (8-10 months) and old (12-18 months) Wistar rats were treated with d-LSD. Animals received 0.13mg/kg of d-LSD via intraperitoneal injections, were housed individually, with an interval of 6 days without treatment before exposure to an object recognition task (ORT). In addition, old rats injected with saline or d-LSD were exposed to EE for 6 days (3h/day) and housed in groups of 5 animals between the last injection and ORT. The ORT was composed of training and test session (30 minutes interval). Two identical objects (assembled using LEGO™ pieces) were used for the training session, with 12 edges and vertices each, for the training session one of the objects was replaced by an object with 14 edges and vertices.

Results and Conclusions: Young animals treated with saline spent in average 59% of the test session exploring the new object, while young animals treated with d-LSD spent in average 76.58±14.77($p = 0.06$) of the test session exploring the new object. Novel object exploration in adult rats increased significantly ($p = 0.0367$) from 43±8.01% (saline) to 64±4.83% (d-LSD), but d-LSD treatment did not change ORT performance in old rats unexposed to EE ($p = 0.99$). Notably, old animals treated with d-LSD and then exposed to EE spent proportionally more time exploring the new object (70.31±8.36%), than old rats treated with saline and exposed to EE (53.38±7.66%, $p = 0.05$). All animals exposed to EE performed better than old animals unexposed to EE (49.77±1.79%). The results suggest that d-LSD improves learning and/or novelty preference, and that old animals can be cognitively enhanced by a combination of d-LSD and EE.

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Individual Differences in Impulsive Action and Temporal Estimation: Interaction with the Serotonin (5-HT) 5-HT_{2A} Receptor

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High impulsivity, or the predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences, pervades numerous neuropsychiatric disorders such as attention deficit hyperactivity disorder, schizophrenia, bipolar disorder, personality disorders, and substance use disorders. Rapid, unplanned reactions suggest an important temporal aspect of impulsivity, and clinical populations with features of high impulsivity tend to under-reproduce and overestimate time on various interval timing tasks. However, preclinical research into the mechanistic relationship between inherent impulsivity and temporal estimation is lacking. Our previous preclinical research demonstrates that serotonin (5-HT) actions at the 5-HT_{2A} receptor (5-HT_{2A}R) modulate impulsive action, and other pre-clinical studies suggest significant effects of 5-HT_{2A}R ligands on behavioral timing. We hypothesized that high trait impulsivity (HI) and low trait impulsivity (LI) would associate with temporal over and under estimation, respectively, mediated by the 5-HT_{2A}R. In the present study, male, Sprague-Dawley rats were evaluated for trait impulsivity in the one choice serial reaction time (1-CSRT) task followed by evaluation of temporal estimation in the interval bisection task (IBT) with pharmacological manipulation of the 5-HT_{2A}R. HI rats demonstrate temporal overestimation in both the 1-CSRT task as well as the IBT relative to LI rats. Furthermore the 5-HT_{2A}R antagonist M100907 reduced impulsive responding and elicited relative temporal under-estimation, whereas the 5-HT_{2A}R agonist 2,5-dimethoxy-4-iodoamphetamine (DOI) increased impulsive responding and temporal over-estimation in the 1-CSRT task and disrupted temporal estimation in the IBT. Collectively, these experiments provide evidence that individual differences in impulsive action are associated with differences in behavioral timing, and that 5-HT_{2A}R modulation affects the temporal aspects of impulsive action as well as temporal estimation.

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POSTRAUMATIC GROWTH IN MDMA-ASSISTED PSYCHOTHERAPY FOR POSTRAUMATIC STRESS DISORDER: RESULTS FROM POOLED PHASE 2 STUDIES

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Background**:** MDMA-assisted psychotherapy for posttraumatic stress disorder (PTSD) has been shown to significantly reduce clinical symptomatology, but posttraumatic growth, positive psychological change experienced after the struggle with highly challenging life circumstances, has yet to be rigorously studied with this treatment. Our aim was to evaluate if such growth, consisting of positive changes in self-perception, interpersonal relationships, or philosophy of life, occurred in MDMA-assisted psychotherapy in addition to PTSD symptom reduction.

Methods**:** Participant data (n = 60) were pooled from three Phase 2 clinical studies employing triple-blind crossover designs. Participants were required to meet DSM-IV-R criteria for PTSD with a score greater than 50 on the Clinician-Administered PTSD Scale-IV (CAPS-IV) and previous inadequate response to pharmacological and/or psychotherapeutic treatment. Data were aggregated into two groups: the active MDMA dose group (75-125 mg of MDMA, n = 45) or the placebo/active control group (0-40 mg of MDMA, n = 15). Measures included the Posttraumatic Growth Inventory (PTGI) and the CAPS-IV, administered at baseline, primary endpoint (one month after the second MDMA or placebo session), and at 12-month follow-up.

Results and conclusions**:** At primary endpoint, the MDMA group demonstrated greater posttraumatic growth than the placebo group (d = 1.08; p = 0.0004) and a greater reduction in PTSD symptom severity (d = 0.62; $p < 0.001$). At the 12-month follow-up, within-subject posttraumatic growth was higher than at baseline ($p < 0.0001$), PTSD symptom severity scores were lower ($p < 0.0001$), and two-thirds of the participants (67.3%) no longer met criteria for PTSD. MDMA-assisted psychotherapy for PTSD resulted in posttraumatic growth and clinical symptom reductions of large magnitude effect sizes. Results suggest that posttraumatic growth may provide a new mechanism of action warranting further study.

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THE FIRST DIRECT PHOSPHORYLATION OF PSILOCIN TO PSILOCYBIN UNDER cGMP CONDITIONS

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Background: The current large-scale manufacturing of psilocybin involves the classical Speeter-Anthony tryptamine synthesis, which is wrought with several formidable challenges, including phosphorylation, hydrogenolysis and multiple recrystallizations. In our quest to circumvent these challenges, we have developed a three-step synthesis of psilocybin under cGMP conditions. The synthesis involves the direct phosphorylation of psilocin to psilocybin, which was found to be operationally simple with high atom-economy, high yielding and optimized for kilogram scale campaign. Furthermore, we will report on the polymorphic forms of psilocybin, dentification, characterization and control of in-process impurities.

Methods: The three-step synthetic route involves a direct phosphorylation of psilocin using phosphorus oxychloride, quenching with binary solvent mixtures (water and tetrahydrofuran) and triturating with warm water of crude reaction mixture; all resulting in psilocybin that meets the required purity specifications. Unlike the previously reported five-step procedure, the new synthetic protocol does not require hydrogenolysis and avoids multiple recrystallizations due to the judicious manipulation of solvent mixtures. The synthesized psilocybin has been structurally authenticated by NMR spectrometric methods, X-RPD analysis and analytical methods using qualified reference standard.

Results and Conclusions:
Psilocybin has been manufactured in kilogram quantity under cGMP conditions to support our FDA controlled Phase 2 clinical trial and research use. A total of 1.21 kg of psilocybin was produced using the new synthetic method.

Candidate Therapeutic Targets for 3,4-Methylenedioxymethamphetamine in the Treatment of Post-Traumatic Stress Disorder

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Background:
While some key components of the biological etiology of Post-Traumatic Stress Disorder (PTSD) have been elucidated over the past 30 years, the inadequacy of pharmacotherapy may reflect that the ultimate biological targets for PTSD symptom reversal have not been identified. As we begin to investigate the putative biological mechanism of 3,4-Methylenedioxymethamphetamine (MDMA), we should (1) consider both how it engages known target systems implicated in PTSD and (2) utilize reverse-translational methods to discover new pathways and circuits relevant to resilience.
Methods:
The PTSD biomarker literature was reviewed. All known pharmacotherapies used in the clinic or in clinical trials were organized into their proposed biological target systems. Information was also gathered about their rationale for use in PTSD and their current status in the clinical treatment of PTSD. The literature on the biologic mechanism of MDMA was also reviewed.
Results:
Treatments were found to engage the following target systems: monoaminergic, glutamatergic, GABAergic, adrenergic, HPA axis, endocannabinoid, opiate, mitochondrial respiration, oxytocin-related, substance-P, nicotinic, protein-synthesis, or enhancing neuroplasticity. The MDMA literature shows some engagement with these systems, but importantly, shifts focus from the mechanism of manipulating dysregulated molecules and pathways associated with PTSD symptoms to producing a substantial change in mental state that increases the ability to engage with traumatic material in psychotherapy.
Discussion:
MDMA-assisted psychotherapy provides a reverse-translational opportunity for the field of biological psychiatry to re-orient mechanistic studies. Perhaps investigating and ultimately enhancing the mechanism of psychopharmacology should focus on its role in optimizing psychotherapy. For example, the pre-clinical literature suggests that MDMA's re-opening of critical widows of neuroplasticity may be important to its efficacy and this work should be explored in human research.

Study funded by MAPS

Anti-Inflammatory and Protective Effects of Topical Ophthalmic (R)-DOI 0.01% in Allergic Conjunctivitis and Recurrent Intermediate Uveitis Disease Models in Rabbits.

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Eleusis Benefit Corporation, New York NY [1], PharmOptima Inc, Portage MI [2], Ophthy-DS Inc., Portage MI [3] Histo-Scientific Research Laboratories, Mount Jackson VA [4]

Background: Recent evidences indicate that (R)-DOI, a 5-HT2R agonist, can inhibit TNFα-induced proinflammatory protein expression (1) and prevent ovalbumin-induced allergic asthma in mice (2). In addition, topical application of (R)-DOI reduced complications from Herpes Simplex Virus-associated ocular disease in mice and rabbit (3). Given the foreseen applications in ophthalmology for a new drug class featuring both steroid sparing and ocular-penetrant anti-inflammatory properties, we set out to investigate the therapeutic viability of topical eye drops (R)-DOI for ocular inflammatory diseases.

Methods & Results:

1/ Ocular and plasma pharmacokinetics of a single topical administration of (R)-DOI 0.1% were determined using LC-MS/MS (LLOQ of 0.1ng/g) in DB rabbits. The observed C_{max} (ng/mL-ng) values were: cornea-10900, iris-ciliary body-7810, conjunctiva-5680, choroid-1240, aqueous humor-297, retina-195, vitreous humor-3.47 and plasma-1.82. The terminal half-life ranged from 35 to 11 hrs in ocular tissues and was 1.9 in plasma. A follow up study established the ability of R-DOI to interact with melanin pigments.

2/ Compound 48/80 was used to induce an anaphylactic response, pruritis, and inflammation modeling allergic conjunctivitis in NZW rabbits. Animal groups were pretreated with topical (R)-DOI 0.05%, 0.01% or 0.001%. (R)-DOI 0.01% demonstrated the most significant inhibition of the allergic response (64% mean inhibition of total clinical score).

3/ Topical (R)-DOI 0.01% was applied TID subsequent to disease induction in the antigen TB-induced recurrent intermediate uveitis model in NZW rabbits. (R)-DOI treatment prevented worsening of vitreous haze (VH) in eyes presenting a mild disease at treatment initiation. Treatment improved time to resolution (VH) in moderate to severely graded eyes by 35% on the primary induction and by ~50% following re-induction. Histopathology assessments at Day 35 revealed decreased intensity of inflammatory cell infiltrates involving the choroid and retina in treated animals as well as a reduced frequency of retinal degeneration.

Conclusions: Topical ophthalmic (R)-DOI 0.01% is readily absorbed into the rabbit eye and effectively reaches both anterior and posterior segments at therapeutically relevant concentrations. Ophthalmic administration of (R)-DOI demonstrated anti-inflammatory efficacy and protection in both anterior and posterior ocular tissues against acute and chronic disease states in allergic conjunctivitis and intermediate uveitis models in rabbits.

Study Funded by Eleusis Benefit Corporation

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Phase I Dose Escalation Study of Psilocybin in Normal Volunteers: Safety and QTc Effects

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PURPOSE: Evaluation of the safety and pharmacokinetics of escalating doses of psilocybin performed under Good Clinical and Laboratory Procedures to support registration trials of the drug.
METHODS: Thirteen healthy adults with prior experience with psychedelics were locally recruited and met all medical and psychological/psychiatric screening criteria. Participants underwent 4-6 hours of preparation with their study guide dyad prior to psilocybin dosing. Participants received monotonically escalating oral doses (0.3, 0.45, and 0.6 mg/kg) of psilocybin at monthly intervals. Blood and urine samples and ECGs were collected to assess pharmacokinetics and QTc effects. Toxicity was assessed and graded using the NCI CTCAE version 4. Participants were followed for 30 days after their last psilocybin dose.
RESULTS: Thirteen participants received at least one dose. One participant was replaced when no blood samples could be obtained after the first dose. One participant was removed before the 2nd dose due to documented white-coat hypertension that prevented him from meeting blood pressure limitations. One participant decided to not receive the 3rd dose due to scheduling difficulties. None of the 10 patients receiving the 0.6mg/kg dose had remarkable toxicities. All participants demonstrated some level of asymptomatic elevated blood pressure after the first psilocybin dose, but the incidence of hypertension decreased with subsequent, higher doses: 100% at 0.3mg/kg, 91% at 0.45mg/kg, 70% at 0.6mg/kg. Asymptomatic bradycardia was more common than tachycardia (7/10 vs 4/10 at 0.6mg/kg, and no relationship was found with dose. There were no reports of hallucinogen persisting perception disorder. There was a weak relationship between plasma psilocin concentrations and the change in QTcF interval.
CONCLUSIONS: Single, escalating oral psilocybin doses of 0.3 – 0.6mg/kg are well tolerated by healthy adults in the research setting. The most commonly reported symptomatic adverse effect is a mild headache arising after the peak effects have dissipated. A transient elevation of blood pressure is common, but it is not clear if this is due to the physiologic effect or reaction to the psychedelic effect of psilocybin. No clinically significant prolongation of QTc is expected from oral psilocybin doses expected in future clinical trials at fixed oral psilocybin doses of 25mg. Psilocybin toxicity types and incidence do not differ significantly from those reported in Phase II trials for depression and substance use disorders.
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Usona Research Institute

Noribogaine is a Potential Treatment for Heroin Addiction

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The United States is currently experiencing an opioid epidemic of epic proportions, and the need for novel treatments for opioid addiction has never been greater. Heroin addiction, a disorder characterized by compulsive drug seeking and relapse, has historically been treated using substitution therapy. That is, the treatment for opioid addiction is often another opioid, such as methadone or suboxone. These therapies have shown tremendous success in reducing heroin use, but achieving the ultimate goal of opioid abstinence can take years, and often, relapse risk escalates after cessation of these therapies. For decades, the success of ibogaine in treating opioid addiction has been undisputed, yet the therapy has never been approved in the United States. This is due, at least in part, to the hallucinogenic properties of this compound derived from the West African shrub, iboga. The primary metabolite of ibogaine, noribogaine, has been demonstrated to have similar effects, but with a better side-effect profile (fewer tremors, etc.). Moreover, often a single treatment is all that is needed to achieve long-term reductions in opioid use and/or relapse, at least with ibogaine. We have previously demonstrated a long-term reduction in cocaine relapse using a single treatment with a different hallucinogen, the kappa opioid agonist U50,488 (Heinsbroek et al., *Neuropsychopharmacology* 2018). The treatment was administered in conjunction with the first extinction training session, which is somewhat analogous to cognitive behavioral therapy in humans, in that animals learn to dissociate the drug seeking response from the reward during the training. In a similar fashion, we are currently investigating the effects of a single treatment with noribogaine prior to the first extinction training session on long-term heroin relapse in a preclinical rat model of opioid abuse. Preliminary data suggest that noribogaine (5 mg/kg, i.p.) does not alter choice for heroin vs. natural reward (i.e. food), nor does it alter heroin consumption when the price of heroin is low (i.e. FR3). However, data collection is underway at the time of submission to determine whether the noribogaine treatment on the first extinction session elicits long-term reductions in heroin relapse.

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Microdosing findings from the Global Drug Survey 2019

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Background: interest in the study of psychedelics such as LSD and psilocybin has resurfaced in the last decade, and while the practice of microdosing – taking sub-hallucinogenic doses – is also growing, there is a paucity of systematic research on the practice of microdosing. This study aimed to replicate our findings from a previous survey, and extend upon it by relating the benefits derived from microdosing to intention – which is canonically important with use of full-dose psychedelics.
Objectives: this pre-registered observational study examined a population of microdosers as part of the most recent Global Drug Survey. We had four hypotheses. H1: The three most common benefits of microdosing will be enhanced focus, better mood, and increased creativity. H2: The three most common drawbacks of microdosing will be concerns about legality, physiological discomfort, and impaired focus. H3: The majority of participants who microdose will not have tested the substance they used to microdose. H4: Participants who report an approach-motivation will report significantly more benefits than participants who report an avoidance-motivation.
Methods: we recruited an online community sample from various online forums, consisting of 3,343 participants with microdosing experience. We used the single-item questions to assess benefits and drawbacks, and also whether participants tested their substances. Microdosing intention was measured using different framing for a few commons motivations. One example for an approach motivation is “to improve mood”; one example for an avoidance motivation is “to escape negative feelings”.
Results: some of our hypothesized benefits and drawbacks were supported by the data. The three most commonly reported benefits were improved mood, creativity and energy. The three most commonly reported drawbacks were none (i.e., no drawback), confusion, and reduced energy. As we hypothesized, most psychedelics users reported not testing their substances, but a surprisingly large proportion did test their substances. Finally, contrary to our hypothesis, approach-motivation to microdosing was predictive of fewer benefits than avoidance-motivation.
Conclusion: these findings provide promising initial evidence that warrants controlled experimental research to directly test safety and efficacy. As microdoses are easier to administer than full-doses, this new paradigm has the exciting potential to shape future psychedelic research.

MDMA-assisted psychotherapy for victims of sexual abuse with severe PTSD in Brazil.

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Objective: Given epidemic violence in Brazil and high prevalence of post-traumatic stress disorder, we conducted the first clinical trial in the country employing MDMA-assisted psychotherapy. Methods: Four of 60 volunteers matched inclusion and exclusion criteria. Three victims of sexual abuse completed enrollment and treatment, following a standardized protocol from previous studies sponsored by the Multidisciplinary Association for Psychedelic Studies (MAPS), with 15 weekly therapy sessions, three with orally administered MDMA spaced about a month apart with concurrent psychotherapy and music. Primary outcome was the monthly CAPS-IV score measured two months after the last MDMA session.

Results: There were no serious adverse events. The most frequent adverse events were somatic pains and anguish. CAPS reductions in all participants were larger than a 25-point drop. Final scores were 61, 27 and 8 from a baseline of 90, 78 and 72, respectively. Reductions were greater than 30% in all three cases, indicative of clinically significant improvements. Secondary outcomes showed reductions in Beck Depressive Inventory and increases in Post-Traumatic Growth Inventory and Global Assessment ofFunctioning.

Conclusions: Considering the current lack of safe and efficacious treatment for PTSD, rising violence in Brazil, and recent studies with larger number of participants treated with this method abroad, MDMA-assisted psychotherapy may become a viable treatment for PTSD in Brazil.

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SEROTONERGIC PSYCHEDELICS EFFECTS ON HIPPOCAMPAL AND PREFRONTAL ELECTROPHYSIOLOGY IN RATS

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Background: The psychoactive effects of classic psychedelics depend on serotonergic receptors 5-HT_{2A} and 5-HT_{1A}, but little is known about their neurophysiological effects. Here we set out to investigate the effects of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) and d-lysergic acid diethylamide (d-LSD), two potent serotonergic agonists, on local field potentials (LFP) recorded from the hippocampus (HP) and prefrontal cortex (PFC) of rats.

Methods: Rats were surgically implanted with a cannula in the lateral ventricle and tungsten (50µm) multi-electrode arrays in the HP and PFC. Experimental sessions consisted of baseline recordings for 1h, injected i.c.v or i.p with 5-MeO-DMT or d-LSD, and recorded for 2-3h or 9h. Electrophysiological signals were recorded with IntanRHD2000, behavior was recorded with CinePlex, and data were analyzed using customized Matlab routines.

Results: Behavioral alterations were observed ~15 min after drug injection, including increased locomotion, increased space occupancy, and the occurrence of stereotyped behaviors such as wet dog shaking, and uncoordinated locomotion. Similar to results from previous studies, LFP alterations were detected in the PFC and the HP. While power in the low gamma band (LG, 20-50 Hz) decreased in both regions within the first 30 min, power in the delta (0.5-5 Hz) band showed an increase in the PFC and a mixed dynamic in the HP, with a delayed increase. Theta (5-10 Hz) power showed a tendency to decrease in the HP. Moreover, phase-amplitude modulation analysis revealed that both 5-MeO-DMT and d-LSD decreased the comodulation of theta phase and gamma amplitude in the HP. Likewise, HP theta and PFC gamma comodulation presented a similar profile. Next, we compared the changes caused by 5-MeO-DMT and d-LSD to the regular electrophysiology of the sleep-wake cycle. State map analysis revealed that both substances promoted a shift in the spectral profile typical of waking towards that of slow-wave sleep, despite the fact that the animals remained overtly awake. While some of these results corroborate previous studies (e.g., the decrease in PFC gamma power), we also found divergent results, such as the increase in PFC delta power. Altogether, the results are novel and promote a better understanding of the neurophysiological alterations caused by psychedelics.

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Introduction to Psychedelic-Assisted Psychotherapy: Theory, Training, Risk Management, and Benefits

PRESENTERS: Shari Taylor, Ph.D, MSN & Mark Skellie, Psy.D.

BACKGROUND: We will review some of the reasoning as to why Psychedelic-Assisted Psychotherapy is recommended versus taking these medicines without professional support. We will discuss our training with the Multidisciplinary Association for Psychedelic Studies (MAPS) for MDMA-assisted psychotherapy for treatment of PTSD and the Compass Pathways training for Psilocybin-Assisted Psychotherapy for treatment-resistant depression. Information will be presented related to mechanisms/details of the protocol as it relates to individual sessions, including music, how placebo sessions are handled, and how suicidality is dealt with. Specific data regarding suicidality in the MDMA-assisted psychotherapy phase 2 studies will be presented.

Our studies enroll patients with severe, chronic PTSD and depression which represents an at risk population for suicide and severe mental issues. Trained professionals are needed to mitigate risk and are better able to contain and respond to whatever may come up. The FDA is currently requiring 2 licensed professionals be in the room during a medicine session and have indicated that this won't be changed until possible post-approval and after more studies have been done. Since licensing boards oversee misconduct, and the premise of MDMA-assisted psychotherapy is that the medicine facilitates therapy, it would stand to reason that outcomes would likely be reduced if therapists aren't properly trained. Future research is needed to compare outcomes across professionals.

We will review approved video clips highlighting aspects of MDMA-assisted psychotherapy and other information from case studies from our work locally. We will also make time for a question and answer session at the end of our presentation.
CONCLUSION: Psychedelic-assisted psychotherapy has opened a novel model for FDA drug approval. We believe that highly trained and credentialed psychotherapists are needed to bring this new model of behavioral health care forward while minimizing risks and maximizing benefits.

SECONDARY OUTCOMES FROM A PILOT TRIAL OF COGNITIVE-BEHAVIORAL CONJOINT THERAPY FOR PTSD WITH MDMA

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Cognitive Behavioral Conjoint Therapy (CBCT) for PTSD was combined with MDMA in an uncontrolled trial of six couples to improve outcomes for individuals with PTSD and their loved ones. Prior reports show large pre-post effect size improvements in PTSD outcomes (e.g., Wagner et al., 2019). One of the aims of the trial was also to see whether there were broader gains for the individual with PTSD and their partner. The 2-month protocol, which included two in-person MDMA-facilitated sessions and non-MDMA CBCT sessions, also included measures of relationship satisfaction, depression, and behavioral accommodation. For the individual with PTSD, there were large, statistically significant decreases in depression (*d*=1.76) which were maintained at 6-month follow-up. They also had large, non-significant increases in relationship satisfaction (*d*=0.83). For the partner without PTSD, they had large, non-significant reductions in behavioral accommodation at post-treatment (*d*=1.12), which became statistically significant at 6-month follow-up (*d*=1.07). Partners also reported non-significant, moderate increases in relationship satisfaction (*d*=0.56). These results suggest that CBCT+MDMA decreases important comorbid symptoms, influences theorized mechanisms of action of PTSD treatments, and improves relationship satisfaction in both partners. Future research will need to replicate these findings in larger samples and using randomized controlled trial methodology.

Study Funded by the Multidisciplinary Association for Psychedelic Studies (MAPS).